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Identifying Predictors of Racial Disparity in Treatment and Mortality Among Patients Diagnosed with Breast Cancer in South Carolina

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IDENTIFYING PREDICTORS OF RACIAL DISPARITY IN TREATMENT AND
MORTALITY AMONG PATIENTS DIAGNOSED WITH BREAST CANCER IN
SOUTH CAROLINA

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DEDICATION

This work is dedicated to God who has been my help all through this program and through my entire life. He has turned my trials into testimonies, and He has made me to be fruitful in all my endeavors. Unto Him alone is all the glory. His goodness and His mercies were my shield all through this program and I appreciate Him for seeing me through in this research work. Though the journey was not easy, but it was worth it.

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ABSTRACT

Introduction: Despite a lower incidence of breast cancer (BrCA) among Black women in the U.S. compared to White women, Black women experience consistently higher mortality rates. The aims of this study were 1) to assess the relationship between race and diagnosis-to-treatment times 2) to assess racial disparity in mortality among Black and White BrCA patients in SC and 3) assessment of the validity of the Mortality-to-incidence ratio (MIR) as a proxy for survival and geospatial investigation of racial disparity among breast cancer (BrCA) patients.

Methods: Breast cancer cases diagnosed between 2002-2010 were obtained retrospectively from the SC Central Cancer Registry, linked with administrative data from a private payor source and Medicaid Plan. The main exposure variable for all analyses was patient's race (White vs Black women). For aim 1, outcome variables were diagnosis-to-treatment time for BrCA-related surgery, radiation, adjuvant hormone treatment (AHT) and chemotherapy; Chi-square tests, logistic regression and generalized linear model analyses were conducted to compare patients' diagnosis-to-treatment times among Blacks and Whites. For aim 2, the main outcome variable was mortality characterized by vital status and total survival time; Cox proportional hazard analyses were conducted to compare hazard ratios among Blacks and Whites to assess disparities in mortality. For aim 3, MIRs were computed from cancer incidence and mortality data which were obtained from the SC Community Access Network (SCAN). ArcGIS 10.2

was utilized to map BrCA MIRs by race (46 counties and 4 regions). MIR were categorized into seven levels using the national BrCA MIR for White women as reference in county maps; in all other maps, categorizations were based on natural breaks in ArcGIS. Survival percentage, Cox Proportional hazard ratios and survival-MIR correlation analyses were computed for all BrCA cases in each county/region utilizing SAS software and data on BrCA cases which were obtained retrospectively from the SC Central Cancer Registry from 2002 to 2010.

Results: A total of 2155 BrCA patients with 1557 White women and 598 Black women were reported in the study period (2002-2010). For aim 1, multivariable linear model regression showed that there was statistically significant increase in adjusted least square means in receipt of AHT by 54 days, 36 days, 63 days and 46 days among unmarried, not being on best chance network and late surgery; multivariable logistic regression showed that the odds of late receipt of surgery was 1.96 (95% CI: 1.38-2.79) among unmarried Black women compared with unmarried White women; 1.89 (95% CI: 1.32-2.71) among Black women who lived ≤ 10 miles to their health providers compared to White women who lived ≤ 10 miles; and 1.40 (95% CI: 1.08-1.82) among Black women who live in urban areas compared with White women who lived in urban areas. For aim 2, multivariable Cox proportional hazard that adjusted for cancer stage showed that the hazard ratio of mortality was 3.45 (1.64, 7.25) among Black women who lived in Low Country region of the state compared with White women who lived in Low Country region of the state. There were no statistically significant differences between White and Black women in the other 3 regions of the state (Midlands, PeeDee and Upstate). For aim 3, there were multiple statistically significant correlations between MIR and survival

overall; MIR and survival among Whites; and Black-White difference in MIR versus Black-White difference in survival (all p-values were <0.05). Low Country region was identified as the region with worse Black-White MIR and survival disparity.

Conclusions: Mortality was higher among Blacks who lived in the Low Country region of the state and among Blacks who lived in urban areas. Health region ranking utilizing the MIR correlated with 12-year survival time in the overall population, Whites and Black-White difference. To improve overall timely receipt of AHT, efforts need to be directed at Black BrCA patients that are not married, not on BCN, and those that received late surgery. To improve overall timely receipt of surgery, efforts need to be directed at Black BrCA patients that are not married, lived in urban areas and lived ≤ 10 miles from their health providers.

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Statistics over the past 20 years in the United States have shown higher mortality rates among Blacks with breast cancer (BrCa) compared to Whites despite lower incidence of BrCa among Blacks. (1-4) In South Carolina (SC), there is a 60% higher risk of Black women dying from BrCa compared to White women (5), with an even higher risk of BrCa mortality among those with a low socioeconomic status. (6, 7) A delay in the commencement of treatment has been hypothesized as one of the possible reasons for the higher mortality among Blacks despite lower incidence over the years. (3) Survival studies have shown that a treatment delay of as little as two months is associated with less favorable survival among BrCa cases. (3, 8, 9)

The mortality-to-incidence ratio (MIR) is a unique way to quantify cancer disparities based on race (5, 10). The MIR is an important indicator that offers additional information beyond what is represented through the individual incidence and mortality rate measures (5), however, few studies have used MIRs to compare cancer rates (5, 11-13). Wagner et al. described racial cancer disparities and their potential geographical determinants by calculating, comparing and mapping MIRs throughout the state of Georgia (GA, United States). This study found that Blacks in GA had more fatal cancers

than Whites for all cancer sites evaluated (10). Furthermore, Sunkara et al. demonstrated a strong linear relationship between the MIR for colorectal cancer and health system rankings across the countries evaluated (14). While there are many advantages to using the MIR as surveillance tool, MIR lacks the ability to capture loss to follow up and censoring. However, survival analyses can capture and account for follow up. Due to this difference between MIR and survival analyses, there is need to conduct sensitivity analyses to compare rankings between MIRs and median survival times across regions in SC by race. This will serve to validate the MIR.

Background

The time from diagnosis to the first course of treatment among cancer patients, including BrCa patients, increased from 1995 to 2005. (15) From 1995 to 2005, there was an increase in average wait time to BrCa surgery from 21 days to 32 days, clearly revealing an increase of 11 days over the years. (16) Diagnosis-to-surgery wait times among BrCa patients in the United States have also increased over the past 20 years. (15, 17, 18) In terms of surgical interventions for BrCa patients, disparities exist between races in wait times from diagnosis to surgery, with significantly higher odds of delayed treatment among Blacks and Hispanics. (18)

The various forms of delay that Black women diagnosed with BrCa experience are related to diagnosis, (19) as well as time to surgery, (3, 20, 21) chemotherapy, (4, 22, 23) adjuvant hormonal therapy,(24-26) and all forms of treatment combined. (27, 28) Documented factors that affect delay in treatment among BrCa by race include age, (28) hospital type, (23) trust in oncologists and communication with physicians. (4) Delays in

adjuvant therapy among BrCa patients have been shown to worsen survival (18, 29) and increase patient anxiety. (18)

Previous studies have utilized the MIR as a surveillance tool and shown that SC exhibits more extreme racial differences in cancer incidence, mortality and MIR than other states or the nation. (30-38) Additionally, examining the MIR helped to highlight health regions where this disparity is highest. (38) The MIR also serves as a population-based approximation of fatality (1/survival) given incidence by stabilizing the incidence and mortality differences across cancer sites and racial groups (5, 10). The MIR is also a unique way to quantify racial cancer disparities (5, 10). Few studies have used the MIR to compare cancer rates (5, 11-13). Wagner et al. described racial cancer disparities and their potential geographical determinants by calculating, comparing and mapping MIRs throughout the state of Georgia (GA, United States) and found that Blacks in GA had higher rates of fatal cancers than Whites for all cancer sites evaluated (10, 14). Strong recommendations have been made for cancer surveillance programs to use MIRs to monitor disparities across racial/ethnic groups and geographic regions (5, 10-14, 38) as a proxy for survival, but there has not yet been a study to assess the effectiveness of MIR as a proxy for survival among BrCa patients, especially in South Carolina where there is marked Black-White disparity. (38)

Proposal and Specific Aims

Effective reduction of disparities in treatment delays and mortality among racial minorities will require the identification of the mechanisms by which these disparities occur. I propose to assess racial disparities in BrCa treatment and mortality in SC by

utilizing data derived from all female BrCa cases over eight years from the SC Central Cancer Registry linked with administrative medical and pharmacy claims data for the Public Employee Benefits Plan (private, state-subsidized insurance plan for state employees) and Medicaid.

This combination of data from both publicly and privately insured BrCa patients will be utilized to assess the complex interplay between geographic factors and racial disparities using Geographical Information System (GIS) mapping, survival methods and multilevel models to identify predictors of treatment delays and mortality that can be intervened upon. GIS methods have been utilized to identify possible predictors of racial disparities in breast cancer survival. (39) However, GIS methodology has not been utilized to specifically identify individual- and area-level characteristics that may contribute to BrCa mortality among Blacks within the context of multilevel survival modeling. Recognition of the causes of disparities in small-area variation in BrCa survival has the potential to allow the application of evidence-based approaches to reduce disparities. (39)

The aims of this study therefore are to 1) assess racial disparities in treatment delays and the utilization of adjuvant hormonal therapy (AHT) among patients diagnosed with breast cancer and 2) identify predictors of dissimilarity in breast cancer-related survival by health regions among Black women in SC utilizing multilevel survival models and GIS methodologies. The above-mentioned dataset will also be used for survival analyses to compute the median survival time for the four health regions in SC in order to rank the health regions. Thereafter, the survival and the ranking derived from the MIRs will be compared.

The Specific Aims

1. To assess racial disparities in breast cancer treatment time in South Carolina (SC).
 - a. To compare wait times from diagnosis to the various forms of treatment in Blacks and Whites with BrCa.
 - b. To assess the effect modifiers (diagnosis year and rural/urban status) that affect the relationship between race (Black vs White) and diagnosis-to-treatment wait times for the different treatment types.

Hypothesis: We hypothesize that the diagnosis-to-treatment wait time is higher among Blacks compared to Whites for all BrCa treatment types in SC. We also hypothesize that diagnosis year and rural/urban status will be an effect modifier in the relationship between race and diagnosis-to-treatment wait times. Assessing for effect modifications between race and important modifiers will also help identify specific modifier groups that help explain the racial disparity among Blacks, which will aid in the development of multilevel interventions.

2. To identify patient- and neighborhood-level predictors of dissimilarity in breast cancer-related survival among Blacks and Whites in SC utilizing multilevel (state and regional) survival models.
 - a. To analyze the breast cancer-specific and overall survival in SC as a whole, as well as by four health regions, utilizing the Kaplan-Meier curve and median survival time.
 - b. To identify predictors of survival by four health regions utilizing the Cox proportional hazard ratios.

Hypothesis: We hypothesize that treatment and mortality outcomes will be worse in Regions 6 and 4, which are characterized by lower socioeconomic status, and will be better in Regions 2 and 7 because of the major hospital systems available in these regions.

3. To compare MIR methodology with survival methodology in assessing racial BrCa disparities over the eight-year period across the four health regions in SC.

- a. Describe BrCa disparities in SC among Blacks and Whites using MIRs by race for the four health regions within SC.
- b. Rank the four health regions by race from the worst to the best using MIRs.
- c. Compute the median survival time by race in the four health regions.
- d. Rank the four health regions by race from the worst to the best using median survival times.
- e. Compare the rankings based on MIRs to those from median survival times to see where differences exist.

Hypothesis: We hypothesize that the findings from MIR by regions will be similar to the survival analyses by regions.

Significance of this study

Although various studies in other states consistently show that Black women with BrCa experience delays in receipt of surgery, chemotherapy, AHT and radiation, (3, 4, 19-23, 27, 28) this has not been examined in SC, which has a high representation of minority and rural populations. SC has well-documented inter-racial differences in cancer

incidence and mortality (30-38). In addition, the possible factors that affect racial disparity in treatment delays in SC have not been examined.

The need to study predictors of disparities in diagnosis-to-treatment times and their effects on survival among BrCa patients in SC is particularly important because Black-White disparity in BrCa mortality is of a higher magnitude in SC (30, 40, 41); mortality among White BrCa patients is 7% lower in SC compared to the national average and is 29% higher among Blacks in SC (30, 40, 41). Also, in SC, mortality from BrCa amongst Blacks is greater than 60% higher than that of Whites (5). Studies also show that Blacks experience worse mortality outcomes after matching for known prognostic factors, and this finding has persisted over time (42-45).

A study that used three cutoff points (30, 60, 90 days) to define a diagnosis-to-surgery delay showed that Black women were more likely to experience delays compared to White women, and this association was independent of health insurance status, age at diagnosis and cancer stage at diagnosis (46). There is therefore a need to assess other factors that influence delay to surgery apart from health insurance, age at diagnosis and cancer stage at diagnosis and to examine how these factors interplay with survival outcomes (21). This study was able to assess other factors such as marital status, county of residence (whether rural or urban), year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), and tumor grade of BrCa at diagnosis.

This study also helped to assess the extent to which radiation treatment guidelines are being adhered to among BrCa patients in SC. For example, the national guideline consensus by the National Institutes of Health (NIH) and American Society of Clinical

Oncology (ASCO) states that BrCa patients who have high risk for locoregional recurrence should receive postmastectomy radiation (PMRT) (47-52). This study helped to assess if PMRT is being adhered to and if racial disparities exists in SC. Additionally, the effect of diagnosis-to-radiation time and surgery-to-radiation time on survival by race in SC added to current body of knowledge (53) in overall survival and BrCa specific survival. This study also helped to assess the extent to which chemotherapy treatment guidelines are being adhered to among BrCa patients in SC. For example, the recommendation from clinical trials is that adjuvant chemotherapy be initiated within 3 months after surgical intervention (54).

Because of the excess contribution of hormone receptor negative (HRN) BrCa patients to mortality among BrCa patients, it is important to study and identify factors that are associated with the receipt of recommended treatment guidelines, inclusive of the recommended 60 days between diagnosis and treatment for BrCa among HRN BrCa patients (55). This information will help guide interventions that will help reduce disparities among Black women (55).

The association between race and commencement of AHT is not well elucidated and appears to be incompletely studied and controversial; thus, further work is required. In North Carolina (NC), statistically significant racial disparity in commencement of AHT has been demonstrated: Blacks were less likely to commence AHT, and this racial disparity was more pronounced among the subpopulation of patients that did not receive chemotherapy. (26) However, in a previous study in SC, there was no racial difference found between Blacks and Whites in the commencement and early use of AHT, but further analysis showed that receipt of chemotherapy/radiation was independently

associated with commencement/early use of AHT. (6) In SC, contrary to the finding in NC, overall use of AHT was worse among patients who received AHT and/or radiation. (6) In the study described above in NC, the BrCa cases were privately insured (26); however, in the study in SC (6), the BrCa cases were on Medicaid insurance. Perhaps the difference in the insurance payer of the BrCa cases between the two studies could help explain the differences in the results. To further understand the interplay between race, commencement of AHT and other forms of treatments for BrCa, there is a need to analyze data on all BrCa cases derived from the Central Cancer Registry linked with administrative medical and pharmacy claims data for the Public Employee Benefits Plan (private insurance) and Medicaid. This study will be able to achieve this.

This study also added to existing body of literature on racial disparities BrCa-specific survival (BSS), (56) and overall survival (OS) (57, 58). Assessment of predictors of survival differences in this study by regions in SC has not been studied before therefore findings from this research will help navigation programs to identify regions with higher racial disparities and also help to identify possible modifiable predictors that are driving the disparities.

The epidemiologic use of the MIR in cancer research is gaining significance and is increasingly used. (5, 10-14, 38) A major drawback of the MIR, however, is that there is no method to account for censoring and loss to follow up. Additionally, the MIR most likely counts the mortality from previous years while using incidence from the current year hence it is not a classic case fatality proportion. It is also not possible to adjust for covariates such as treatment, comorbidities or individual socioeconomic status in MIR analysis. Another weakness is that the relationship between the numerator (mortality) and

the denominator (incidence) may not be direct because persons diagnosed with BrCa may not die of BrCa, and persons who die after the diagnosis of BrCa will survive for varying lengths of time, which the MIR cannot account for.

The limitations of the MIR described above make it difficult to compare results of MIR studies directly with those of survival studies. Survival studies are more complex, time-consuming and expensive and require more skills to carry out. Using MIR is less time-consuming, less expensive and requires fewer skills to carry out. (5) The potential utility of the MIR in cancer surveillance programs for monitoring disparities across racial/ethnic groups and geographic regions is substantial, as shown by previous studies. (5, 10, 12, 14, 38) It is therefore important to see how the MIR compares with survival studies in identifying racial disparities and in ranking health regions for the purpose of surveillance.

This study found that the health region rankings are similar whether using MIR or survival time, hence it may be preferable to use the cheaper, faster and less time-consuming MIR, which also requires fewer skills, to identify racial disparities and rank health regions to identify areas that require urgent attention/interventions. To our knowledge, this is the first study that sought to directly compute MIR by health regions and compare this ranking with a ranking produced by median survival time to further substantiate the usefulness of the MIR in resource-poor settings and in quick decision making to identify areas that need urgent interventions.

Additionally, a previous report shows that predictors that are environmental in nature affect health and disparity, (59) but the influence of geographical factors has not

been well explored among younger women. This is particularly important because young Black women (less than 65 years old) present with relatively more fatal BrCa, leading to higher mortality among this group. (30, 40) This proposed project aims to focus on this relationship among the target population.

Overall, the study population (SC) being considered in this study is unique because of the high proportion of SC residents that live in rural areas and the high racial disparity found in SC in other studies. The proposed analytic techniques in this study are also unique because the MIR has not been utilized to assess BrCa disparities in SC and this will be the first study conducting a direct sensitivity analyses comparing MIR with survival analyses both on the state-wide level and regional level. Identifying predictors of racial differences in survival by regions is also unique as findings has the potential to help guide more result-oriented navigation efforts.

CHAPTER 2

LITERATURE REVIEW

Disproportionate Breast Cancer Burden among Blacks

Despite the awareness and funding dedicated to closing the racial gap in cancer therapy, it is discouraging to note that racial disparities persist in BrCa mortality (60, 61). Compared with non-Hispanic Whites, Blacks bear an excessive public health burden of BrCa in the United States (1, 2, 62). Mortality due to BrCa is encountered at a much higher rate among Blacks compared to Whites (40, 63, 64). Mortality from BrCa is about 40% higher among Blacks compared to Whites, although Whites have a higher likelihood of being diagnosed with BrCa (6, 65, 66). The lifetime probability of developing BrCa is 1 in 9 among non-Hispanic Whites and 1 in 8 among Blacks. However, the lifetime probability of dying from BrCa is 1 in 37 among non-Hispanic Whites but 1 in 31 among Blacks (2). The mortality rate from BrCa is 22 per 100,000 among non-Hispanic Whites and 31 per 100,000 among Blacks (2).

Although the Black-White disparity in BrCa mortality is seen both at the national level and in SC specifically, the disparity is of a higher magnitude in SC (30, 40, 41); mortality among White BrCa patients is 7% lower in SC compared to the national average and is 29% higher among Blacks in SC (30, 40, 41). Also, in SC, mortality from BrCa amongst Blacks is greater than 60% higher than that of Whites (5). Studies also

show that Blacks experience worse mortality outcomes after matching for known prognostic factors, and this finding has persisted over time (42-45).

Results from meta-analyses of BrCa that were conducted in 2002 and 2006 showed that there was about 20% excess risk of death among Blacks compared to Whites (67, 68). The pooled hazard ratio of mortality among Blacks compared with Whites was 1.22 (95% C.I.: 1.13-1.30) in 2002 and 1.28 (95% C.I.: 1.18-1.38) in 2006 (67, 68). The meta-analysis revealed that there were clear survival disadvantages among Blacks with BrCa in all studies considered (67, 68).

Factors that Contribute to Higher Mortality among Black BrCa Cases Compared to Whites

Identified factors that contribute to a higher mortality among Blacks compared to Whites in the US are socioeconomic status, tumor biology (more aggressive tumors), disability, environmental factors, comorbidities, cultural differences, late stage at diagnosis and age at diagnosis (21, 22, 41, 69-77). Severe obesity and high waist-to-hip ratio among Blacks have also been found to contribute to racial differences in stage at BrCa diagnosis, as Blacks had a higher likelihood of severe obesity and being in the highest tertile of waist-to-hip ratio (64).

Blacks also have various barriers to accessing care and have been shown to consistently receive lower-than-recommended BrCa care when compared with their White counterparts (21, 25, 43, 61, 73, 78). This includes lower-than-recommended rates of radiation after surgical treatment for BrCa (25, 43, 61, 78). Blacks have also been

shown to be 30-40% more likely to receive BrCa treatments that are not in line with guidelines across all BrCa subtypes (79).

Socioeconomic status (SES) has been identified as one of the main drivers of racial disparities in BrCa mortality, as women in low socioeconomic levels tend to present with more advanced-stage BrCa, which usually has poorer prognosis (71, 80). Generally, the five-year survival rate is worse among population subgroups with lower SES, which are usually comprised of a large proportion of Blacks (71, 81). Whereas about 12% of Whites live below the poverty level, this proportion is 26% among Blacks (71, 82).

Previous studies have also shown that there is a tendency among Blacks to not receive preventative services such as early screening mammograms (77). Blacks are also likely to have BrCa with low pathologic complete response (pCR) to chemotherapy (56). pCR has been shown to be a major prognostic index, as higher pCR has been linked with better survival outcomes (56). Blacks have also been shown to have a larger median tumor diameter at presentation and also to present with triple-negative BrCa (TNBC) (83).

Treatment Guidelines for Breast Cancer

The national guideline consensus by the National Institutes of Health (NIH) and American Society of Clinical Oncology (ASCO) states that BrCa patients who have high risk for loco-regional recurrence should receive post-mastectomy radiation (PMRT) (47-52). For stages I and II BrCa, there are two recommended forms of treatment: lumpectomy i.e., breast conserving surgery (BCS), followed by whole-breast radiation

therapy; and a modified form of a radical mastectomy with or without radiation therapy (78, 84, 85). PMRT is indicated only when the tumor size is large and three or more lymph nodes are affected (43, 84-86). A study that assessed the recurrence of BrCa comparing women with lumpectomy without radiation therapy and women with lumpectomy with radiation therapy showed recurrence rates of 14% and 39%, respectively, among the two groups (53).

Both forms of treatments for stage I and II BrCa have been shown to lead to similar outcomes (53) in overall survival, disease-free survival and distant disease-free survival. An additional recommendation for women with hormone receptor-positive (HRP) BrCa is that those women with progesterone-positive (PR) or estrogen-positive (ER) BrCa receive AHT for five years post diagnosis. (43, 85). This recommendation is particularly useful for all BrCa that is 1 cm or greater in size. Irrespective of the stage or size of the BrCa, the guideline recommends that ER or PR status should be determined (43, 85).

A predefined cutoff of 60 days was set by the National Breast Cervical Cancer Early Detection Program (NBCCEDP) between an abnormal screening test and diagnosis and between diagnosis and initiation of treatment (21, 60, 74). The cutoff set by NBCCEDP is that BrCa patients who experience delays of more than 60 days in initiation of treatment should not comprise more than 20% of all BrCa patients (21, 60, 74). The NBCCEDP has seen some success in the initiation of treatment for BrCa as a result of this benchmark (8, 60, 87).

Definition and Importance of Treatment Delays among BrCa Patients

The treatment interval was defined as the time in days between diagnosis of BrCa and initiation of treatment, as in Caplan et al., Connors et al. and McLaughlin (8, 74, 88). The date of diagnosis was defined as biopsy date, which was utilized as a proxy for biopsy-confirmed BrCa diagnosis (8, 74, 88). The date of initiation of treatment was defined as the date of definitive surgery, the date of initiation of neoadjuvant chemotherapy or the date of initiation of AHT (8, 74, 88). For surgical treatment, definitive surgery was determined as the most invasive surgery of the primary BrCa site (74, 89). Examples of definitive surgeries include mastectomy, lumpectomy, excisional biopsies and re-excision of the site of biopsy (74, 89).

Other authors have referred to the treatment interval by other names, such as treatment delay or delay interval (90, 91). Past categorizations of treatment intervals have used 4 groups, i.e., ≤ 30 , 31-59, 60-69 and >90 days (74, 89). Another author used the term time to primary treatment (TPT) to describe period between the date of pathological diagnosis and the date of primary treatment (92). BrCa patients have also been defined as having a treatment delay if they had a treatment interval greater than 60 days (74, 89). As mentioned above, those patients who experience delays greater than 60 days should not comprise more than 20% of the total patients, according to NBCCEDP (21, 60, 74). However, studies show that delays greater than 90 days have the potential to lead to worse BrCa outcomes, especially poorer survival (8, 54, 74, 93).

The diagnosis-to-treatment interval is an important quality measure that is recognized by the National Accreditation Program for Breast Centers (NAPBC), the

American Society of Breast Surgeons (ASBS) and the National Quality Measures for Breast Care (NQMBC) (94-96). The NAPBC, ASBC and NQMBC all serve to validate breast cancer care rendered by hospitals (94-96). However, there has been no formal agreement on what constitutes an acceptable delay in terms of quality of BrCa care measures (94-96). Another reason that the diagnosis-to-treatment wait time is important is that studies have shown one of the most overwhelming, distressing and anxiety-producing periods for BrCa patients is the waiting time between an abnormal mammogram and treatment initiation (94, 97).

Racial Disparities in the Receipt/Delay in the Receipt of Recommended Treatments

Generally, disparity in the utilization of various treatment forms such as surgery, radiotherapy, chemotherapy and AHT has been hypothesized as the cause of the disproportionate increase in mortality from BrCa (21, 77, 98). There is a higher likelihood that a Black woman will experience treatment delay and/or discontinuation of treatment for BrCa when compared with a White woman (46, 90, 99). Fedewa et al. found that irrespective of stage of BrCa at diagnosis, age and the health insurance status of the BrCa patient, Blacks had a higher likelihood of delay in receipt of treatment for BrCa (46). Another study also showed that the odds of a Black BrCa patient experiencing diagnosis-to-treatment delay beyond 1 month were 1.6 times (95% C.I.: 1.4-1.9) those of White women (90).

A study in Missouri showed that the median diagnosis-to-treatment wait time for any first course of treatment among Blacks was 27 days and that about 12% of Black women had treatment delays above 60 days (74). In North Carolina, the median

diagnosis-to-treatment wait time was 22 days (8). Similar results were also seen internationally, as a study in Malaysia found that the median TPT was 18 days, and most of the BrCa patients' primary treatment was surgery (92).

Surgery

To define a delay, a predefined cutoff of 60 days was set by the NBCCEDP between abnormal screening test and diagnosis and also between diagnosis and initiation of treatment, which is surgery in most BrCa cases (21, 60). Compared with White women, a large proportion of Blacks do not undergo surgical intervention for invasive BrCa (72). There has also been an increase over time in the diagnosis-to-surgery wait time among Medicare patients from 29 days (1992) to 32 days (2006) (16). In addition, another study showed that time to surgery increased over time from a mean of 22 days (1998) to 31 days (2003) to 41 days (2008) (100). A study assessing the effect of race on diagnosis-to-treatment time showed that about 15% of Blacks experienced treatment delay (≥ 6 weeks) compared to about 8% of White women (9). Sheppard et al. showed that the mean diagnosis-to-treatment time for Blacks and Whites were 47 days and 33 days, respectively, and that Black women were 58% less likely to have surgery within 90 days (21).

A study that used three cutoff points (30, 60, 90 days) to define a diagnosis-to-surgery delay showed that Black women were more likely to experience delays compared to White women, and this association was independent of health insurance status, age at diagnosis and cancer stage at diagnosis (46). Another study that utilized a cutoff point of 60 days showed that the odds of Black women experiencing a delay were 3.0 (C.I.: 1.9-

5.0) compared to White women (98). There is therefore a need to assess other factors that influence delay to surgery apart from health insurance, age at diagnosis and cancer stage at diagnosis and to examine how these factors interplay with survival outcomes (21). Some of the factors that were identified as delaying the interval from diagnosis to surgery were ordering an MRI, systemic imaging, the type of surgery to be performed, patient choice and plastic surgery consultation (17). In terms of type of surgery, a study found that the mean time from consultation to lumpectomy was 22 (± 16) days, the mean time to mastectomy was 37 (± 29) days, and the mean time to mastectomy with reconstruction was 38 (± 16) days (101). Other factors that were identified as influencing late receipt of surgery among Blacks were mode of detection, health insurance and tumor size (98).

Radiotherapy

Radiotherapy is recommended for stage I and II BrCa patients following BCS; however, Black women and other racial/ethnic minorities usually do not receive radiotherapy (25, 78, 91). Local recurrence of BrCa has been shown to be higher among patients that had BCS without concomitant radiotherapy (72, 102). Studies have shown that there were disparities in the receipt of radiotherapy by racial/ethnic minorities, as the odds of Black women experiencing radiation delay were 1.92 (95% C.I.: 1.55-2.37) compared to White women (78, 103). Black women with BrCa had a higher likelihood of receiving delayed radiotherapy after surgery compared to White women (98). Delay in receipt of radiation was defined as receiving radiotherapy at least 8 weeks after surgery (103).

Freedman et al. hypothesized some possible reasons for the racial disparities, including distance to treatment sites, inability to get time off work, childcare and limited transportation (78). Another possible reason that racial/ethnic minorities may not receive radiation therapy is that doctors may feel that the risks outweigh the benefits in older patients. However, after excluding older women (>69 years old) from their study, Freedman et al. still saw striking disparities affecting racial/ethnic minority groups, suggesting that there are other reasons for the disparities besides age (78).

Adjuvant Hormone Therapy (AHT)

Adjuvant hormonal therapy (AHT) has been shown to improve both short- and long-term survival among HRP BrCa patients worldwide, as it reduces BrCa mortality and reoccurrence by 33% and 40%, respectively. (104) Annually, over 100,000 women diagnosed with BrCa are classified as HRP, which has the potential of being cured (69, 105) if BrCa patients commence and adhere to treatment with AHT. United States National Guidelines for the use of AHT recommends that women with HRP BrCa receive AHT for 5 years (85, 106, 107). AHT is a prescription oral medication, and studies show that current rates of adherence are between 50% and 75%, and most BrCa patients discontinue the medication within the first year after prescription (108-112).

The advantages of AHT notwithstanding, 10-30% of eligible BrCa patients never start treatment with AHT, (113, 114) and many who start AHT never adhere to or complete the treatment, (111, 112, 115) leading to recurrence and increased mortality. (116) Specifically, a study in New Zealand showed that suboptimal usage of AHT led to increased BrCa mortality and recurrence among a specific ethnic group in New Zealand

compared to Whites. (117) However, the association between race and commencement of AHT is not well elucidated and appears incompletely studied and controversial; thus, further study is warranted.(6, 26)

Assessment of AHT use

There are various ways to assess use of AHT among BrCa patients. One method is to assess if a BrCa patient ever used AHT (6). Patients referred to as ever-users are those who have at least one pharmacy claim record for any AHT medication during the study period (6). Determination of ever use of AHT can be done by utilizing records in the registry data or the pharmacy claims data, including claims for tamoxifen or aromatase inhibitors such as exemestane, letrozole and anastrozole (6, 69, 118-123).

Another way to assess the use of AHT is to determine early/late initiation of AHT after a diagnosis is made (6). In this case, patients who received AHT within 12 months of diagnosis are categorized as early users, and those that started treatment with AHT after 12 months will be categorized as late users (6).

A third mechanism to determine use of AHT is the medication possession ratio (MPR) (6, 69, 112, 114, 115, 124). MPR here is defined as the AHT prescription supply per unit time (days) for the year following the start of AHT (or until data is censored by disenrollment). In order to calculate the MPR, the numerator is the total days covered by the medication (using total day supply) and the denominator is the number of days for which the supply is needed (69, 112, 114-116, 121-123). A ratio of more than 80% is usually classified as adherence to treatment (114, 125).

Another method to assess AHT use is adherence, which is further divided into duration of treatment, persistence and consistent daily use of AHT (126). Adherence to prescribed AHT is the degree to which a patient's behavior in taking AHT corresponds with the medical recommendation (126). Persistence is the time period for which a patient continues to fill prescriptions after the initial filling, and the interval between prescription refills is usually measured and reported (114, 125-127). Prescription rate has also been utilized to assess use of AHT and is estimated as a minimum of one pharmacy-filled prescription for one of the AHT medications within one year of the diagnosis of BrCa (114).

Chemotherapy

The recommendation from clinical trials is that adjuvant chemotherapy be initiated within 3 months after surgical intervention (54). Diagnosis-to-chemotherapy time was shown to be longer for Blacks compared to Whites, and this observed difference was shown to be higher among women that had their cancer care transferred from other health care providers to National Comprehensive Cancer Network (NCCN) institutions after the diagnosis was made (128). The racial disparity was also more marked among women that were on Medicare compared with women on commercial insurance (128).

A study by Fedewa et al. showed that the mean time from surgery to receipt of adjuvant chemotherapy was 41 (± 24) days (89). In this study, 85% and 96% of patients received adjuvant chemotherapy within 60 and 90 days, respectively, of surgery (89). The odds that a Black woman receives late treatment, defined as treatment after 60 days of receipt of surgery, were 1.6 (95% C.I.: 1.4-1.7) (89) compared to Whites. Apart from

race, other factors that contributed delayed receipt of chemotherapy were presence of comorbidities, the type of facility where the treatment was received, insurance status/type of the patient and stage at diagnosis (89).

Survival Assessments in BrCa Patients

There are different types of outcomes that have been studied in BrCa patients (57, 129). Some of the most studied outcomes are overall survival (OS), BrCa-specific survival (BSS), BrCa progression-free survival (BPFS), (57, 129) and distant metastasis-free survival (DMFS) (56). Usually, in cancer registry data, vital status and survival duration are relatively error-free, but the cause of death is sometimes not accurate, as some studies have shown that the underlying causes of death not coded as BrCa-related deaths may actually be associated with BrCa treatment-related deaths or are due to BrCa complications (57, 58). Some studies therefore have preferred OS rather than BSS (57, 58). When it is not feasible to compare treatment types on the basis of OS, BPFS, which is the time from randomization to progression or death, has been utilized as an acceptable primary endpoint (129).

Effects of Inadequate or Delayed Treatment on Survival among BrCa Patients

A delay in receipt of BrCa treatment has been associated with reduction in BrCa survival (74-76). Delays of three or more months have been associated with low 5-year survival compared with patients who did not experience such a delay (41, 93). Delays that are less than 90 days have not been generally reported to affect survival in a negative way (92, 94). However, another study that assessed delay in TPT (with the most frequent

primary treatment being surgery) using a cutoff point of 30 days did not find a statistically significant association between TPT and OS (92).

Similar findings in North Carolina showed that diagnosis-to-treatment wait time did not have an association with OS when patients were diagnosed with early stage BrCa; however, the association was significant among BrCa patients that were diagnosed at late stages (8). In this study, the cutoff that to determine late receipt of treatment was 60 days (8). Women who had late-stage BrCa and received their first course of treatment at/after 60 days after diagnosis had increases of 66% and 85% in their risk for all-cause and BrCa-specific mortality, respectively (8). Therefore, delays of greater than 90 days were significantly associated with poor survival in all patients, whereas delays of greater than 60 days were statistically significant among late-stage BrCa patients alone (8, 92, 94).

However, there was also a study that utilized 90 days as a cutoff point to determine delay in receipt of first definitive treatment for BrCa that did not find a significant association with OS (94). The reason given for the possible difference between this study and other studies that found significant associations with OS was the way in which the delay interval was calculated (94). Whereas other studies utilized onset of symptoms as the starting point, Brazda et al. utilized date of tissue diagnosis as the starting point (93, 94, 130).

Effect of Diagnosis-to-Surgery Time on Survival

Delay in breast cancer diagnosis-to-surgery time has been associated with disparities in breast cancer outcomes (9, 21, 93, 131, 132). BrCa patients who had surgical intervention 12 weeks after diagnosis or later had worse survival when compared

with those who had surgery within 1-4 weeks (132). Poorer survival outcomes were associated with delays greater than 3-6 months among symptomatic women and 6 weeks among younger women (21, 93). 90% of women that had a diagnosis-to-surgery time of <2 weeks survived to 5 years, whereas 80% of women that had a diagnosis-to-surgery time of >6 weeks survived to 5 years (9).

The negative effect of a diagnosis-to-surgery delay is more striking among Black women, who tended to have public or no insurance and were usually of lower SES (9, 21). When delays from diagnosis-to-surgery time were assessed using cutoffs less than 6 weeks in some studies, mixed results were produced (21, 131, 133). A study that was carried out among TNBC patients showed that interval to treatment did not affect overall survival; however, there was a trend towards poor survival among patients with delays greater than 90 days (131). It has also been shown that longer diagnosis-to-chemotherapy time is associated with poorer survival outcome (54, 93).

Effect of Diagnosis-to-Radiotherapy/Surgery-to-Radiotherapy Time on Survival

The national guideline consensus by the NIH and ASCO states that BrCa patients who have high risk for locoregional recurrence should receive PMRT (47-52). Lack of receipt of radiation therapy following BCS has been shown to lead to increased mortality among BrCa patients (114, 134). In a North Carolina study among Medicaid-enrolled women, higher mortality was observed among women who did not get radiotherapy after BCS (134). These women who did not get radiotherapy had higher odds all-cause and BrCa-specific mortality of 2.4 and 4.5, respectively (134). However, another study by Shi et al. found that PMRT used alone was not statistically associated with mortality risk in

multivariate analyses (135). In terms of the effect of time from surgery to radiotherapy on survival, a study showed that BrCa patients with an interval greater than 7 months had a worse 6-year distant metastasis-free survival (56).

Effect of Diagnosis-to-Chemotherapy Time on Survival

BrCa patients who have delay in initiation of chemotherapy have significantly reduced 10-year survival (136). A study by Downing et al. utilized both traditional regression analyses and latent class analysis and found that women who had the longest wait to chemotherapy had the poorest 5-year survival (137). A meta-analysis conducted utilizing 7 studies showed that a 4-week increase in time to initiation of adjuvant chemotherapy was associated with significant decrease in OS and DFS (138).

Effect of Diagnosis-to-AHT Time on Survival

Inadequate adherence to AHT has been shown to reduce survival among BrCa patients (114, 126, 139). A study that assessed the effect of race on mortality outcomes noted a significant interaction between race and HRP BrCa cases in predicting mortality (41). The study further showed that Blacks with hormone receptor–negative (HRN) BrCa had a higher risk of death, with a hazard ratio of 4.0 compared to their White counterparts. Thus, hormone receptor status serves as an effect modifier in the relationship between race and mortality (41). Another study found that HRN BrCa patients still had poorer survival even after accounting for SES and access to healthcare (55).

Factors that Affect Diagnosis-to-Treatment Wait Times and Survival Outcomes

(Independent predictors, potential confounders and potential effect modifiers)

Independent predictors of longer diagnosis-to-surgery time that are socioeconomic in nature are advancing age, Black or Hispanic race, lack of insurance/Medicaid insurance, low level of education, living in urban areas, higher number of comorbidities and stage 0 and grade 1 disease (18). Facility-related independent predictors are high-volume facilities and research/academic facilities (18). Having to wait longer than 30 days to receive surgical intervention was a predictor of delay in the receipt of adjuvant chemotherapy greater than 60 days, meaning that one delay led to another delay (18).

Age

Most BrCa cases occur in women that are above the age of 49 years; however, BrCa patients that are younger have higher mortality and higher prevalence of factors leading to poor outcomes (65, 72). Women with BrCa that are younger than 36 years old are likely to have larger tumors, greater involvement of lymph nodes, higher stage disease, poorly differentiated tumors and HRN tumors (140).

Factors that lead to poorer outcomes in younger women include larger-sized tumors, grade, involvement of lymph nodes, less HRP tumors, tumors with poorer grade, tumors with higher level of recurrences, higher S-phase fractions and higher likelihood of aneuploidy tumors (72, 140). All these factors lead to worse BrCa-specific and overall survival among younger BrCa patients (72, 140). In addition, these factors that lead to

worse survival outcomes among younger women with BrCa are more prevalent among Black women than White women (72).

Enrolment in Best Chance Network (BCN) Program

The BCN is an early detection program in South Carolina for breast and cervical cancer (41, 141). Women that are eligible for this program are those that are aged 47-64 years, residents of SC, underserved/underinsured or do not have insurance and are of low income (less than 200% of the Federal poverty level). This program provides free breast and cervical cancer screening and started because SC has one of the highest rates of uninsured women the United States (40, 41, 141). Recruitment into the BCN program is usually through active search by federally qualified health centers, the South Atlantic Division, media outlets and through outreaches carried out by the American Cancer Society. Women that are enrolled in BCN are usually of low socioeconomic status and are likely to experience treatment delays (41, 141).

In St. Louis, Missouri, an evaluation of BrCa patients referred to the National Cancer Institute's designated Comprehensive Cancer Center (NCI-CCC) showed that women that were referred from a scheme similar to the BCN called the safety net system experienced greater delays in treatment initiation compared to women that were referred from private healthcare systems (74-76). The women that were on the safety net systems also had a higher likelihood of being diagnosed with advanced-stage BrCa (74-76).

Socioeconomic Status

There are multiple ways in which SES can contribute to BrCa disparities. One way is that those that are economically disadvantaged are unlikely to take advantage of screening efforts because of associated costs. This would lead to presentation of advanced BrCa among this group, thus creating large diagnostic delays and barriers to comprehensive care (65, 71). Another way that SES leads to racial BrCa disparities is that Blacks tend to disproportionately receive less of the treatments recommended by various guidelines, such as locoregional treatment, sentinel lymph node biopsy, reconstruction treatment for the breast, adjuvant radiotherapy and systemic adjuvant therapy, and they are less likely to participate in randomized clinical trials (71, 79, 142, 143).

Interestingly, a study in North Carolina showed that poverty was a modifier in the effect of non-receipt of radiotherapy following BCS, as poor women who did not receive radiotherapy had 2.4 and 4.5 increased all-cause and BrCa-specific mortality, respectively, compared with non-poor women (134). This could be because poor women are likely to have more comorbidity, present with advanced-stage disease and forego annual surveillance mammography and are more likely to be geographically isolated from adequate care (134).

One of the ways in which SES has been measured in past studies is utilization of neighborhood-level, area-level or Census –tract–level poverty (55, 57). In California, Haji-Jama et al. found that BrCa patients who lived in neighborhoods designated as poor have worse survival and that Blacks that lived in these poor neighborhoods had a 21% higher likelihood of worse survival compared to Whites (57). It was also shown that the

average difference between the annual income of Whites and Blacks in these poor neighborhoods was \$14,575; hence, it is possible that Black uninsured women lacked the ability to cover out-of-pocket expenses associated with seeking care for BrCa (57, 144).

Hormone Receptor Status and Receipt of Adjuvant Hormonal Therapy

Beyond SES, the disproportionate burden of BrCa experienced by Blacks has also been partly attributed to biological factors, for which hormone receptor status can serve as a proxy (55, 65, 67, 105, 124, 145). The incidence rate of TNBC, which is a determinant of poor prognosis, has been shown to be much higher among Blacks compared to Whites (71, 79, 124, 145). In addition, the incidence of BrCa among women aged 45 years and below, which is also associated with poor prognosis, is higher among Blacks compared to Whites (71, 72, 105).

Additionally, studies have shown that after controlling for SES and stratifying by stage at diagnosis, there is a still residual disparity in the cancer burden that is unfavorable to Blacks when compared with Whites (65, 67). This points to the fact that there are biological factors that contribute to the Black-White disparity in BrCa outcomes. The role of biological factors has been buttressed by other studies that show that Black women of African descents (not born in the US) in Britain also have higher prevalence of TNBC compared with their White counterparts (71, 83, 146, 147).

Insurance Type

Insurance type has been shown to be a contributor to the differences in treatment noted between Blacks and Whites (72). As a result of the Affordable Care Act (ACA), an

additional 20 million US citizens obtained health insurance coverage; however, disparities in health insurance coverage still exist (71, 82). 24% of Blacks are currently uninsured, whereas that percentage is 8% among Whites (71, 82). A study by Smith et al. showed that 18% of BrCa patients with no health insurance/public health insurance had a delay of greater than 6 weeks in diagnosis-to-surgery wait time compared with only 10% of those with private health insurance (9).

Stage at Diagnosis

A greater proportion of Blacks are diagnosed with later-stage disease (148). The odds of presenting with late-stage disease among Blacks is 1.5-folds higher than among Whites (148). Blacks have a 30-60% higher likelihood of being diagnosed with a stage II-IV BrCa when compared to Whites (79).

Type of Surgery

The scheduled type of surgery has also been found to influence the diagnosis-to-treatment wait time (74, 128). It has been shown that women who were scheduled for breast reconstruction surgery experienced increased treatment delays (74, 128). In addition to experiencing delays from diagnosis-to-treatment wait times, these BrCa patients have a higher likelihood of having surgical complications, which may lead to further delays in the initiation of other adjuvant systemic therapies (74, 128, 149, 150).

Marital Status

Mosunjac et al. found that unmarried women with BrCa experienced greater delays from diagnosis to BCS compared to married women (151). The mean time to BCS

was 70 days for married women and was 93 days for unmarried women; this difference was statistically significant (151).

County (Rural versus Urban Status)

Rural versus urban status of BrCa patients has been implicated as a factor that affects the distribution of late-stage diagnosis (148). Women that lived in non-metropolitan counties had a higher likelihood of presenting with late-stage BrCa compared with those who lived in metropolitan counties (148).

Mortality-to-Incidence Ratio (MIR)

The MIR is a unique way to assess racial cancer disparities (5, 10). The MIR is an important indicator that offers additional useful information beyond what incidence and mortality rates alone can provide in a study (5, 38). Some studies have utilized MIR methodology to compare cancer rates (5, 11-13). Wagner et al. previously described racial cancer disparities and the potential geographical determinants of cancer by calculating, comparing and mapping MIRs throughout the entire state of Georgia (GA, United States) and found that Blacks in GA had relatively more fatal cancers than Whites for all cancer sites evaluated (10). Sunkara et al. also demonstrated a strong linear relationship between the colorectal cancer MIR and health system rankings across the various countries evaluated (14).

Mapping of MIRs across SC Department of Health and Environmental Control (DHEC) health regions has been utilized in past studies in SC (5, 38). SC DHEC currently defines four health regions for the purpose of planning environmental and

health programs. A sensitivity analysis described previously by Sunkara et al. (152) examined the effect of moving across different “denominator years” to vary with the alignment of the average incidence-to-mortality time interval. The sensitivity analysis used all combinations of sex and race for cancers involving all anatomic sites. It was shown that the lines describing the MIR remained parallel, with the rates generally remaining stable over time across eight different 5-year periods beginning in 1996. This analysis was performed using incidence data from the SC Central Cancer Registry (SCCCR) (152).

As a ratio with the mortality rate as the numerator and the incidence rate as the denominator, the MIR takes on numeric values ranging from 0 to 1. Values closer to 0 indicate more indolent cancers, whereas those closer to 1 indicate more aggressive cancers. The MIR, which has been shown to be highly insensitive to time-discordant incidence and mortality (152), does not take into account follow-up time and is not equivalent to Cox proportional hazards–type survival analysis, which is a truly multivariate technique that accounts for follow-up time. Similarly, the MIR cannot account for competing risk.

Computing the MIR

In past studies, in order to compare racial differences in MIRs in SC DHEC health regions, four categories of MIR were computed (5, 38). First, the MIR for a specific cancer of interest was computed for Whites nationally (93) (i.e., for the US as a whole from the United States Cancer Statistics at the Centers for Disease Control and Prevention) as a reference. The upper limit of Category 1 was the reference; the upper

limit of Category 2 was 10% higher than the reference; the upper limit of Category 3 was 20% higher than the reference; and Category 4 consisted of MIRs >20% higher than the reference. This method of categorization and analysis was used previously by Hebert et al. and Babatunde et al. (5, 38) The defined categories of each DHEC health region were mapped by race using ArcGIS Version 10.1 (ESRI, Redlands, CA) .

Importance of the MIR in Cancer Surveillance

Using the MIR as a surveillance tool in a past study underscores the point that SC exhibits more extreme racial differences in cancer incidence, mortality and MIR than other states or the nation (30-37), and specifically, the MIR helped highlight regions where this disparity is highest (38). For example, in this past study, Regions 6 and 4 in SC have the highest MIR disparity, where the MIRs of Blacks are 3.1 and 3.0 times higher, respectively, than those of Whites. Regions 6 and 4 encompass the Pee Dee region, which is known for its lower socioeconomic status, rurality and being medically underserved (5). Additionally, in four of the 12 counties in the Pee Dee regions (Dillon, Lee, Marlboro and Williamsburg), over 40% of adults report a BMI of 30 or more (153). Similarly, the percentage of adults aged 20 and over reporting no leisure-time physical activity was greater than 30% in seven counties (Chesterfield, Darlington, Dillon, Lee, Marion, Marlboro and Sumter) out the 12 counties in the Pee Dee region (153). Urban centers with major hospital systems such as Charleston (Region 7), Columbia (Region 3), Greenville and Spartanburg (Region 2) may be responsible for the relatively smaller MIR disparities seen in Regions 2 and 7 in the previous study (38).

The MIR serves as a population-based approximation of fatality (1/survival) given incidence by stabilizing the incidence and mortality differences across cancer sites and racial groups (5, 10, 38). One of the advantages of MIR analyses lies in the fact that it gives researchers the opportunity to use combined data over many years with minimal data request protocol; this makes MIR estimates more stable (38). Data used for MIR analyses usually help mitigate problems associated with migration of patients in and out of a jurisdiction/state. This is because of the interjurisdictional exchange agreements between states to capture out-of-state deaths of residents. Also, MIR analyses usually involve a population-based study of the entire population of patients, whereby incidence and mortality data represent >94% of all cancer cases. Thus, the study is virtually devoid of selection bias, a common problem associated with such studies. Additionally, the MIR is cheap and easy to compute from existing relatively complete data. The MIR can be used as a surrogate measure for a more expensive and time-consuming survival studies (38).

Drawbacks of the MIR Necessitating Need for a Sensitivity Analyses

A main drawback of the MIR, however, is that there is no way to compute censoring and loss to follow up. It is also not possible to adjust for covariates such as treatment, comorbidities or individual socioeconomic status in the analysis. Another weakness is that the relationship between the numerator (mortality) and the denominator (incidence) may not be direct because persons diagnosed of with cancer may not die of cancer and persons who die after the diagnosis of cancer may survive for varying lengths of time, which cannot be accounted for by the MIR (84). A sensitivity analysis comparing

regional survival with MIR analyses will therefore validate the use of the MIR in surveillance.

CHAPTER 3

METHODS

Data Source

This study was a retrospective cohort study (2002 to 2009) that included data on all BrCa patients derived from linked files from the SCCCR and Office of Revenue and Fiscal Affairs (which maintains the administrative medical claims data for the South Carolina Public Employee Benefits plan and Medicaid). The study was exempt from IRB review by the University of South Carolina IRB. All newly diagnosed cases of cancers were collected by SCCCR, which is a population-based system in SC. Data in the SCCCR included information on demographics, diagnosis date, cancer location and histology, treatment and overall survival. (38) All incident cancer cases were required by law to be reported to SCCCR, a resource established with funding from an award from the National Program of Cancer Registries (NPCR) in 1994. Enabling legislation from the SC General Assembly was enacted in 1996. Data are collected by SCCCR on all cancers, both *in-situ* and invasive, from hospitals, pathology laboratories, freestanding treatment centers and physician offices. The only exceptions are *in situ* forms of cervical cancer and invasive forms of basal and squamous cell skin cancers of non-genital sites.

The SCCCR from which we derived the data for this analysis has a history of receiving the highest/gold rating for data completeness (>94%), timeliness and data quality from the North American Association of Central Cancer Registries and NPCR.

SCCCR is a member of the CDC National Interstate Data Exchange System (N-IDEAS), such that any member state may share resident incident cases with others to ensure the completeness of incident cancer data. Additionally, there was geocoding of all cancer cases and cancer deaths in the state of SC.

The SC Revenue and Fiscal Affairs Office (RFA) is an independent agency that houses administrative claims data from both SC State Employee Health Plan and SC Medicaid plan members. The RFA developed a series of algorithms using various combinations of personal identifiers to create its own unique identifier, enabling statistical staff to “link across” multiple providers and settings. Hence, it allowed for linkages while protecting the confidentiality of the client. The SC Revenue and Fiscal Affairs Office and SC Central Cancer Registry frequently work together to complete data linkage requests for researchers in SC. All BrCA cases between the time period of 2002 to 2010 who met eligibility criteria (that could be ascertained from their files) were given to RFA. Then RFA matched to determine which cases linked and further met our eligibility criteria (that required claims data to ascertain). This resulted in the 2155 cases. This resulting combined dataset was used to conduct all analyses.

Data Linkage and Security

Linkages were made with 3 personal identifiers: name, date of birth and social security number. As per protocol, these linkages were performed by RFA in partnership with SCCCR. Because of data security issues, only the final de-identified dataset was released to study personnel and investigators for analysis. The key to the de-identified dataset was retained by RFA in the event that further data clarifications are needed from

the primary record. Once the de-identified data were received, the study data manager performed routine outlier and logic checks. Any improbable values were verified with RFA or SCCCR and rectified where possible. To create an analytic dataset, we utilized datasets from the RFA (Medicaid and State Health Plan), BCN and SCCCR to create an extensive look at breast cancer treatment in South Carolina for Black and White women. Data acquisitions were linked through the aforementioned departments by the RFA, and only a study participant number was assigned to each person for analysis by investigators. Because the final dataset was completely de-identified, the investigators have no linkages to the original identifiable patient contact information and will be referred to via a study participant number only.

Variables

Aim 1

For aim 1, the main predictor variable was race of the BrCa cases, dichotomized as Black or White. The main outcome variable was time from diagnosis to various forms of treatment, i.e., surgery, AHT, chemotherapy and radiotherapy. Outcome variables were treated as numeric variable (days) or dichotomized variables (early and late) depending on whether they met the assumptions for a linear model. Variables that were considered as covariates or effect modifiers are age, marital status, county of residence (whether rural or urban), year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), stage of BrCa at diagnosis and grade of BrCa at diagnosis.

Aim 2

For aim 2, the main predictor variable was race of the BrCa cases, dichotomized as Black or White. The main outcome variable was time until death. Variables that were considered as covariates or effect modifiers are age, marital status, county of residence, year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), stage of BrCa at diagnosis and grade of BrCa at diagnosis.

Outcome Variables. *Overall and breast cancer mortality:* We utilized vital status, total survival time, and BrCA cause of death (yes/no) for this investigation. From cause of death information, we were able to examine both all-cause/overall mortality, as well as BrCa-specific mortality.

For survival analyses, the main predictor variable was race stratified by region, categorized as Upstate, Midlands, Low Country and Pee Dee. Survival analyses were carried out in each of the four regions and ranked using hazard ratios. Possible covariates or effect modifiers are age, marital status, county of residence, year of diagnosis, hormone receptor status, stage of BrCa at diagnosis, grade of BrCa at diagnosis, race of the BrCa cases dichotomized as Black or White, receipt of AHT dichotomized as yes/no, early/late receipt of AHT, and BCN dichotomized as yes/no.

Aim 3

This study described BrCA disparities in SC among Blacks and Whites using MIRs by race for the four health regions and by 46 counties within SC. We proceeded to rank the four health regions by race from the worst to the best using MIRs. MIR were computed from Cancer incidence and mortality data which were obtained from the SC

Community Access Network (SCAN) for 1996 to 2016 (county maps) and 2002 to 2010 (regional maps). In order to compare racial differences in BrCa MIRs in the four SC DHEC health regions, seven categories (for county maps) of BrCa MIRs were defined. First, the MIR were computed for Whites nationally (93) (i.e., for the US from the United States Cancer Statistics at the Centers for Disease Control and Prevention) as a reference. The upper limit for Category 1 was the reference; the upper limit of Category 2 was 10% higher than the reference; the upper limit of Category 3 was 20% higher than the reference; the upper limit of category 4 was 30% higher than the reference; the upper limit of category 5 was 40% higher than the reference; the upper limit of category 6 was 50% higher than the reference and Category 7 consisted of MIRs >50% higher than the reference. This method of categorization and analysis was adapted from a previous study by Hebert et al. and Babatunde et al. (5, 38)

Project Design and Analysis Plan

Aim 1

Overall goal: We assessed racial disparities in treatment delays among patients diagnosed with BrCa.

Approaches of the dissertation research project: The main outcome variable were diagnosis-to-treatment time (overall and by various treatment modalities, i.e., surgery, AHT, chemotherapy and radiotherapy), which were defined as the interval between the date of diagnosis and the date of first treatment for the four forms of treatment. The main exposure variable was the patient's race (White vs Black). Race will be determined by the Central Cancer Registry Records, which are based on self-reported

data collected by hospitals and providers. Student's t-test with a significance level of 0.05 were used to assess differences in diagnosis-to-treatment times by patient's race. The outcome variables were checked for normality and other linearity assumptions. If linearity assumptions were met, a generalized linear model will be used to compute least-square means and 95% C.I.s for each dependent variable (surgery wait time, AHT wait time, radiation wait time and chemotherapy wait time) comparing those Blacks with Whites after adjustment for age, marital status, county of residence, year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), stage of BrCa at diagnosis and grade of BrCa at diagnosis. Observations with elevated studentized residuals and Cook's D values were removed from the analyses.

When linearity assumptions were not met, we dichotomized the four outcomes into early and late receipt of treatment using the cutoff as determined from the median in the univariate analyses of the outcome variables. When this latter option was used, we fitted a logistic regression model to compare early to delayed receipt of treatments with the goal of identifying important predictors of treatment delay for each dependent variable (surgery, AHT, radiation and chemotherapy) comparing Blacks with Whites after adjustment for age, marital status, county of residence, year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), stage of BrCa at diagnosis and grade of BrCa at diagnosis.

Aim 2

Overall goal: Identification of patient- and neighborhood-level predictors of dissimilarity in BrCa-related survival among Blacks utilizing multilevel (state and regional) survival models among BrCa patients.

Approaches of the dissertation research project:

For aim 2, Kaplan-Meier survival curves were used to assess BrCa-specific and all-cause survival at the state and regional levels. The relationships between race, mortality rates, diagnosis-to-treatment times and all covariates will be assessed using the Cox proportional-hazards model. A backward elimination process was utilized to obtain the best model. Individual-level, (30) and health region–level (i.e., four health regions comprised of contiguous counties located in SC) (38) factors have been shown to make contributions to the pervading cancer disparities experienced by minority groups. A combination of geospatial methods and multilevel survival modeling helped to objectively identify individual-level and health region–level predictors of survival. The use of GIS and related spatial methodologies has the potential to identify environmental/neighborhood predictors of health outcomes, and this technique is increasing in popularity. (154, 155) Predictor variables/covariates that were considered with survival analyses are age, marital status, county of residence (urban or rural), year of diagnosis, hormone receptor status, enrolment in BCN (dichotomized as yes or no), stage of BrCa at diagnosis and grade of BrCa at diagnosis.

Aim 3

Overall goal: To compare MIR methodology with survival methodology in assessing racial BrCa disparities over the eight-year period across the four health regions in SC.

Rationale:

Survival analysis: Overall survival rates was estimated using Kaplan-Meier techniques. 5-year and 12-year overall survival and BrCA specific survival were estimated and corresponding 95% confidence intervals were calculated. Cox Proportional hazard models were used to evaluate the impact of race on overall survival while adjusting for potential confounders.

MIR: BrCa MIRs by race (Black vs. White) will be computed for years 2002-2010. Years 2002 to 2010 will be utilized to mirror the years of registry data that were obtained for the survival analyses. The age-adjusted incidence and mortality rates will first be calculated using incidence and mortality data from SCCCRC. MIRs will be stratified by race, specifically Blacks versus Whites. As a ratio with the mortality rate in the numerator and the incidence rate in the denominator, the MIR takes on values ranging from 0 to 1. Values closer to 0 indicate more indolent cancers, whereas those closer to 1 indicate more aggressive cancers. The MIR, which has been shown to be highly insensitive to time-discordant incidence and mortality (152), does not take into account follow-up time and is not equivalent to Cox proportional hazards-type survival analysis, which is a truly multivariate technique that accounts for follow-up time.

Computing the MIR

This study described BrCA disparities in SC among Blacks and Whites using MIRs by race for the four health regions and by 46 counties within SC. We proceeded to rank the four health regions by race from the worst to the best using MIRs. MIR were computed from Cancer incidence and mortality data which were obtained from the SC Community Access Network (SCAN) for 1996 to 2016 (county maps) and 2002 to 2010 (regional maps). In order to compare racial differences in BrCa MIRs in the four SC DHEC health regions, seven categories (for county maps) of BrCa MIRs were defined. First, the MIR were computed for Whites nationally (93) (i.e., for the US from the United States Cancer Statistics at the Centers for Disease Control and Prevention) as a reference. The upper limit for Category 1 was the reference; the upper limit of Category 2 was 10% higher than the reference; the upper limit of Category 3 was 20% higher than the reference; the upper limit of category 4 was 30% higher than the reference; the upper limit of category 5 was 40% higher than the reference; the upper limit of category 6 was 50% higher than the reference and Category 7 consisted of MIRs >50% higher than the reference. This method of categorization and analysis was adapted from a previous study by Hebert et al. and Babatunde et al. (5, 38)

Comparison of MIR and survival

The health region–specific MIRs by race were compared with survival by race in each health region to see if the MIR is a true approximation of survival. *The hypothesis is that the median survival time will be a mirror image of the MIR for each of the eight health regions in SC.* All statistical analyses will be performed using Statistical Analysis

Systems software, version 9.2 (SAS Inc., Cary, NC). All hypothesis testing will be 2-sided with a $p < 0.05$ level of statistical significance.

A study that I led in the past (38) utilizing MIRs as a proxy for survival under the supervision of my mentor showed that MIR helped highlight regions where endometrial cancer (EC) disparity was highest. For example, Regions 6 and 4 have the highest MIR disparity in EC, where the MIRs of Blacks are 3.1 and 3.0 times higher, respectively, than those of Whites. In SC, Regions 6 and 4 encompass the Pee Dee region, which is known for its lower socioeconomic status, rurality and being medically underserved (5). Additionally, in four of the 12 counties in the Pee Dee region (Dillon, Lee, Marlboro and Williamsburg), over 40% of adults report a BMI of 30 or more (153). Similarly, the percentage of adults aged 20 and over reporting no leisure-time physical activity was greater than 30% in seven counties (Chesterfield, Darlington, Dillon, Lee, Marion, Marlboro and Sumter) out of the 12 counties in the Pee Dee region (153). Also in this study, (38) urban centers with major hospital systems such as Charleston (Region 7), Columbia (Region 3), Greenville and Spartanburg (Region 2) may be responsible for the relatively smaller MIR disparities seen in Regions 2 and

CHAPTER 4

RACIAL DISPARITIES AND DIAGNOSIS-TO-TREATMENT TIME AMONG PATIENTS DIAGNOSED WITH BREAST CANCER IN SOUTH CAROLINA

Introduction

A delay in the commencement of treatment has been hypothesized as one of the possible reasons for the higher mortality among Blacks despite lower incidence over the years. (3) Survival studies have shown that a treatment delay is associated with less favorable survival among BrCA cases. (3, 8, 9) Although the Black-White disparity in BrCA mortality is seen both at the national level and in SC, the disparity is of a higher magnitude in SC (30, 40, 41): mortality among White BrCA patients is 7% lower in SC compared to the national average and is 29% higher among Blacks in SC (30, 40, 41). Also, in SC, mortality from BrCA amongst Blacks is greater than 60% than that of Whites (5). Studies also show that Blacks experience worse mortality outcomes after matching for known prognostic factors, and this finding has persisted over time (42-45).

The various forms of delay that Black women diagnosed with BrCA experience are related to diagnosis, (19) as well as time to surgery, (3, 20, 21) chemotherapy, (4, 22, 23) adjuvant hormonal therapy, (24-26) and all forms of treatment combined. (27, 28) Documented factors that affect delay in treatment among BrCA by race include age, (28)

hospital type, (23) trust in oncologists and communication with physicians. (4) Delays in adjuvant therapy among BrCA patients have been shown to worsen survival (18, 29) and increase patient anxiety. (18)

Although various studies in other states consistently show that Black women with BrCA experience delays in receipt of surgery, chemotherapy, AHT and radiation, (3, 4, 19-23, 27, 28) this has not been examined in SC, which has a high representation of minority and rural populations. SC has well-documented inter-racial differences in cancer incidence and mortality (30-38). In addition, the possible factors that affect racial disparity in treatment delays in SC have not been examined.

The aim of this study was to assess racial disparities in BrCA treatment time in South Carolina (SC) by comparing diagnosis-to-treatment times for the various forms of treatment in Blacks and Whites with BrCA and to assess related effect modifiers. We hypothesize that the diagnosis-to-treatment wait time is higher among Blacks compared to Whites for all BrCA treatment types in SC.

Methods

Data Source

This is a retrospective cohort study (2002 to 2010) that included data on all BrCA patients derived from linked files from the SC Central Cancer Registry (SCCCR) and Office of Revenue and Fiscal Affairs (which maintains the administrative medical claims data for the South Carolina Public Employee Benefits plan and Medicaid). The dataset was deidentified, hence the study was exempt from IRB review by the University of

South Carolina's IRB. All newly diagnosed cancer cases are collected by SCCCR, which is a population-based cancer registry in SC. Data in the SCCCR include information on demographics, diagnosis date, cancer location and histology, treatment and overall survival. (38)

The SCCCR has a history of receiving the highest/gold rating for data completeness (>94%), timeliness and data quality from the North American Association of Central Cancer Registries and NPCR. SCCCR is a member of the CDC National Interstate Data Exchange System (N-IDEAS), such that any member state may share resident incident cases with others to ensure the completeness of incident cancer data. Additionally, there is geocoding of all cancer cases and cancer deaths in the state of SC.

The SC Revenue and Fiscal Affairs Office (RFA) developed a series of algorithms using various combinations of personal identifiers to create its own unique identifier, enabling statistical staff to "link across" multiple providers and settings. Hence, it allows for linkages while protecting the confidentiality of the client. All BrCA cases between the time period of 2002 to 2010 who met eligibility criteria (that could be ascertained from their files) were given to RFA. Then RFA matched to determine which cases linked and further met our eligibility criteria (that required claims data to ascertain). This resulted in the 2155 cases. This resulting combined dataset was used to conduct all analyses.

Because of data security issues, only the final de-identified dataset was released to study personnel and investigators for analysis. The key to the de-identified dataset was retained by RFA if further data clarifications are needed from the primary record. Once the de-identified data was received, there was a performance of routine outlier and logic

checks. Any improbable values were verified with RFA or SCCCRC and rectified where possible. To create an analytic dataset, we utilized datasets from the RFA (Medicaid and State Health Plan), Best Chance Network (BCN) and SCCCRC to create an extensive look at BrCA treatment in South Carolina for Black and White women. The BCN is an early detection program in South Carolina for breast and cervical cancer (41, 141). Women that are eligible for this program are those that are aged 47-64 years, residents of SC, underserved/underinsured or do not have insurance and are of low income (less than 200% of the Federal poverty level).

Inclusion and Exclusion Criteria

To qualify for inclusion in the analytic sample, the BrCA cases were those diagnosed as a first primary cancer between 2002 and 2010, had a form of insurance (either Medicaid or state health plan) at the time of diagnosis and had 36 months of continuous eligibility on the insurance. This was to ensure that treatment data was available for at least 36 months post diagnosis for each case.

Variables

The main predictor variable was race, dichotomized as Black or White. Race variable was self-reported as determined by the SCCCRC records. The main outcome variable was time from diagnosis to receipt of first treatment for various forms of treatment, i.e., surgery, AHT, chemotherapy and radiotherapy. The first treatment received was determined and the number of days from diagnosis to the treatment modality was also determined. New variables designated diagnosis-to-treatment time for each of the four forms of treatment were created. Outcome variable for AHT was treated

as numeric because records met the assumptions for a linear model using skewness and kurtosis of -2 to +2 when assessed by race.

The outcome variable for chemotherapy, radiotherapy and surgery were dichotomized variables (early and late) because they did not meet the assumptions for linear models. The cut-off for dichotomization was based on the median for the distribution which was 22, 60, and 60 for surgery, chemotherapy and post-surgery radiotherapy respectively. Variables that were considered as covariates or effect modifiers were age, marital status, urban vs. rural designation (based on rural urban commuting codes/RUCA 2003), year of diagnosis (2002-2004, 2005-2007, 2008-2010), hormone receptor status (positive or negative), enrollment in BCN (dichotomized as yes or no), stage of BrCA at diagnosis (insitu, local, regional, or distant), grade of BrCA at diagnosis (well differentiated, moderately differentiated, poorly differentiated and undifferentiated) network distance to health care provider (in miles), definitive surgery type (lumpectomy or mastectomy), early/late surgery (early or late), and insurance provider (provider 1 or provider 2). One of the health insurance provider categories was Medicaid, while the other one was private (State Employee Health Plan); the specific payer source was not identified in the analytic dataset as per data use agreements specified by the payers.

Analysis

A generalized linear model was used to compute least-square means and 95% CIs for AHT (dependent variable that met linear assumptions) comparing Blacks with Whites after adjustment for age, urban versus rural designation, year of diagnosis, hormone receptor status, enrollment in BCN (dichotomized as yes or no), stage of BrCA at

diagnosis, and distance to providers. In assessing the relationship between race and time to AHT, we assessed for the presence of effect modifiers and marital status, being enrolled in BCN, late surgery and insurance providers were identified as effect modifiers: the multivariable generalized linear model therefore was stratified by the effect modifier variables.

The variables that did not meet linearity assumptions (chemotherapy, radiotherapy and surgery), were dichotomized into early and late receipt of treatment using 22 days for surgery, 60 days for chemotherapy and post-surgery radiation. Two-way interactions were assessed between the all predictor variables and race. There was statistically significant interaction between race and marital status, race and urbanicity, and race and distance. The multivariable logistic model was stratified by the effect modifier variables and each model was adjusted for age, year of diagnosis, hormone-receptor status, stage, grade, and being in BCN.

In assessing the relationship between race and time to post-surgery radiation, the identified effect modifiers were age, hormone-receptor status and insurance provider. The multivariable logistic model was stratified by the effect modifier variables and each model was adjusted for marital status, urban status, year of diagnosis, stage, grade, distance to providers and early/late receipt of surgery. In assessing the relationship between race and time to chemotherapy, the identified effect modifiers were urban status and early/late surgery. The multivariable logistic model was stratified by the effect modifier variables and each model was adjusted for age, marital status, diagnosis year, stage, grade, distance, insurance provider, and definitive surgery type.

Results

Descriptive statistics for this study sample are shown in Table 1. Overall, there were 2155 cases of BrCA patients of which the majority were Whites (1557, 72.25%). In bivariate analyses, there were significant differences between Blacks and Whites in age, rural/urban status, year of diagnosis, hormone receptor status, cancer grade, cancer stage and insurance provider. Blacks were more likely to be in age group 45-54 (45.99%) while whites were more likely to be in age group 55-64 years (41.88%). Blacks were more likely to be unmarried (57.17%) compared to Whites (29.95%). The proportion of Whites that live in urban area (79.13% vs 67.22%) and have hormone receptor positive cancer (81.03% vs 68.89%) is higher among whites compared to blacks. More blacks were participants in BCN compared to Whites (9.87% compared with 3.85%).

Table 2 presents diagnosis to hormone treatment times by marital status, being in BCN, early surgery and insurance provider. Multivariable generalized linear model regression analysis showed that the least square means from diagnosis to surgery were statistically increased among Blacks that were not married (54 days), Blacks that were not on BCN (36 days), Blacks that had late surgery later than 30 days after diagnosis (42 days), Blacks that had surgery later than 60 days after diagnosis (63 days) and Blacks that were on insurance provider 1 (46 days) adjusting for age, diagnosis year, hormone-receptor status, stage, grade, urban status, and distance to provider.

Multivariable logistic regression that adjusted for 8 variables (age, year of diagnosis, hormone receptor status, cancer stage, cancer grade, being in BCN, definitive surgery type and insurance provider) showed that the odds of late receipt of surgery was

1.96 (95% CI: 1.38-2.79) among unmarried black women compared with unmarried white women; 1.89 (95% CI: 1.32-2.71) among blacks who lived ≤ 10 miles to health providers compared to whites who lived ≤ 10 miles; and 1.40 (95% CI: 1.08-1.82) among blacks who live in urban areas compared with white women who lived in urban areas (Table 3).

Table 4 presented the results of race by late receipt of post-surgery radiation stratified by age, hormone receptor status and insurance provider in which each model adjusted for marital status, urban status, diagnosis year, stage, grade, distance, definitive surgery type and receipt of early/late surgery. The only significant finding upon multivariable modeling was that black women were less likely to receive late post-surgery radiation (OR: 0.30; CI: 0.10-0.93) compared to white women which implies that the odds of white women with hormone receptor negative BrCA receiving late post-surgery radiation was 3.3 (CI: 1.07-10.28).

Table 5 presented the results of race by late receipt of chemotherapy stratified by urban status and late/early surgery. Each model adjusted for age, marital status, diagnosis year, stage, grade, distance, insurance provider and definitive surgery type. Multivariate analysis did not show any significant finding.

Discussion

This study demonstrated that there was a longer diagnosis-to-treatment time for all treatment modalities for Blacks when compared with Whites. Late receipt of AHT was higher among blacks that were unmarried, received late surgery, and not a participant of

the BCN. We also found that late receipt of surgery was higher among blacks that were unmarried, lived in urban areas and those who lived less than 10 miles to their health care provider. The only sub-group where whites had a later receipt of treatment was for post-surgery radiation among hormone receptor negative BrCA patients. In addition to showing that there were longer diagnosis-to-treatment time in which has been demonstrated from previous studies, (18, 22, 26, 74, 128) we were able to add the following to the racial disparity discussion: the impact of being unmarried, living in urban areas, enrolment in BCN, and distance on late receipt of treatment. This study also showed the positive relationship between late receipt of surgery and time to AHT demonstrating that those who are late to receive one form of treatment are likely to be late at the receipt at other forms of treatment. The use of the findings in this paper has the potential to further enhance the understanding of navigation of health care process and strengthen navigation efforts aimed at linking women with BrCA to care especially among blacks thereby reducing racial disparities.

In analysing the longer diagnosis-to-treatment time in receipt of AHT, this study had a cohort that contained patients on Medicaid and patients on a private payor health plan which made the findings more representative compared with previous studies that was among Medicaid only or private insurance only and which had different findings in racial disparities (6, 26). These previous studies showed that the association between race and commencement of AHT is not well elucidated and appears to be incompletely studied and controversial; thus, our work provided a further understanding of the relationship. In North Carolina (NC), statistically significant racial disparity in commencement of AHT was demonstrated: Blacks were less likely to commence AHT,

and this racial disparity was more pronounced among the subpopulation of patients that did not receive chemotherapy. (26) However, in a previous study in SC, there was no racial difference found between Blacks and Whites in the commencement and early use of AHT, but further analysis showed that receipt of chemotherapy/radiation was independently associated with commencement/early use of AHT. (6) In the study described above in NC, the BrCA cases were privately insured (26); however, in the previous study in SC (6), the BrCA cases were on Medicaid insurance. Because our study had both groups of insurance providers, it provided a further understanding showing that racial disparities existed in receipt of AHT with blacks entering care at least about 17 days later after adjustments were made for age, year of diagnosis, stage, grade, urban status and distance to provider.

A study that used three cutoff points (30, 60, 90 days) to define a diagnosis-to-surgery delay showed that Black women were more likely to experience delays compared to White women, and this association was independent of health insurance status, age at diagnosis and cancer stage at diagnosis (46). Additionally, studies have shown that after controlling for socio-economic status and stratifying by stage at diagnosis, there is still residual disparity in the cancer burden that is unfavorable to Blacks when compared with Whites (65, 67). Our study provided an additional insight into this topic by assessing other factors that influence a longer diagnosis-to-treatment time for surgery apart from health insurance, age at diagnosis and cancer stage at diagnosis (21). Our study showed that unmarried black women were more likely to have a longer diagnosis-to-treatment time in receipt of surgery and AHT. Our finding is like that of Mosunjac et al. which found that unmarried women with BrCA experienced greater delays from diagnosis to

breast conserving surgery compared to married women (151). The mean time to BCS was 70 days for married women and was 93 days for unmarried women; this difference was statistically significant (151). Our study also added to the literature with our finding that among women who lived in urban areas and who lived less than 10 miles to their health care providers, black women were likely to receive late surgery.

The diagnosis-to-treatment interval is an important quality measure that is recognized by the National Accreditation Program for Breast Centers (NAPBC), the American Society of Breast Surgeons (ASBS) and the National Quality Measures for Breast Care (NQMBC) (94-96). The NAPBC, ASBC and NQMBC all serve to validate BrCA care rendered by hospitals (94-96). Although, there has been no formal agreement on what constitutes an acceptable delay in terms of quality of BrCA care measures (94-96), our study demonstrated racial disparities in diagnosis to treatment in the receipt of surgery and AHT. Another reason that the diagnosis-to-treatment wait time is important is that studies have shown one of the most overwhelming, distressing and anxiety-producing periods for BrCA patients is the waiting time between an abnormal mammogram and treatment initiation (94, 97). Our study therefore helped to identify subgroups of BrCA patients that may benefit from more intensive navigation to care in order to shorten the diagnosis-to-treatment times for various BrCA patients.

Our finding that late surgery predicted late receipt of AHT is similar to previous studies where having to wait longer than 30 days to receive surgical intervention was a predictor of longer diagnosis-to-treatment time in the receipt of adjuvant chemotherapy greater than 60 days, meaning that one delay led to another delay (18). This is a finding that has a potential implication for navigation programs that perhaps additional efforts

need to be planned to link people who have already experienced one form of delay along the care continuum, so they do not continue to be delayed in other forms of treatment that has the potential to enhance survival.

Our findings show that Blacks who were not enrolled in the BCN experienced a longer diagnosis-to-treatment time in receipt of surgery. The BCN is an early detection program in South Carolina for breast and cervical cancer (41, 141). Women that are eligible for this program are those that are aged 47-64 years, residents of SC, underserved/underinsured or do not have insurance and are of low income (less than 200% of the Federal poverty level). This program provides free breast and cervical cancer screening and started because SC has one of the highest rates of uninsured women the United States (40, 41, 141). Recruitment into the BCN program is usually through active search by federally qualified health centers, the South Atlantic Division, media outlets and through outreaches carried out by the American Cancer Society. Women that are enrolled in BCN are usually of low socioeconomic status and are likely to experience longer diagnosis-to-treatment time (41, 141). In St. Louis, Missouri, an evaluation of BrCA patients referred to the National Cancer Institute's designated Comprehensive Cancer Center (NCI-CCC) showed that women that were referred from a scheme similar to the BCN called the safety net system experienced longer diagnosis-to-treatment time in treatment initiation compared to women that were referred from private healthcare systems (74-76). The women that were on the safety net systems also had a higher likelihood of being diagnosed with advanced-stage BrCA (74-76). Since, our findings showed that there is a longer diagnosis-to-treatment time in receipt of AHT between Blacks and Whites that are not on BCN but no difference between Blacks and Whites on

BCN, it therefore suggests that, perhaps the BCN program in SC is helping to close the racial disparity gap between Whites and Blacks or those who are on BCN have other factors that is driving the racial disparities. This will benefit from future studies.

One strength of this study is the availability of a wide range of effect modifiers and covariates that were utilized in the analysis. To our knowledge, this is the first study that assessed all 4 treatment modalities among both privately and publicly insured patients using both multivariate logistic regressions and multivariate generalized linear models (depending on distribution of outcome data) with specific emphasis on assessing effect modifiers in SC, which has a high representation of minority and rural populations. Our study was also able to analyze the role of distance to health care provider in late receipt of treatment. Limitations of this study include inability to study biological factors that contribute to the Black-White disparity in BrCA outcomes. The role of biological factors has been buttressed by other studies that show that Black women of African descents (not born in the US) in Britain also have higher prevalence of triple negative BrCA compared with their White counterparts (71, 83, 146, 147).

In conclusion, late receipt of AHT was higher among blacks that were unmarried, received late surgery, and not a participant in BCN. We also found that late receipt of surgery was higher among blacks that were unmarried, lived in urban areas and those who lived less than 10 miles to their health care provider. There is a longer diagnosis-to-treatment time in receipt of AHT between blacks and white that are not on BCN but no difference between blacks and white on BCN, it therefore suggests that, perhaps the BCN is helping to close the racial disparity gap between whites and blacks or those who are on BCN have other factors that is driving the racial disparities. The relationship between

being on BCN and diagnosis-to-treatment time in receipt on AHT will benefit from future studies as it will be important to understand the reason for the longer time among those not on BCN. To improve overall timely receipt of AHT, efforts need to be directed at Black BrCA patients that are not married, not on BCN and received late surgery. To improve overall timely receipt of surgery, efforts need to be directed at Black BrCA patients that are not married, lived in urban areas and lived ≤ 10 miles from health providers.

Table 4.1 Summary of patients' characteristics by race

		N (%)	N (%)	N (%)	
Characteristic		Total (N=2155)	White N=1557 (72.25)	Black N=598 (27.75)	P
Age (mean±SD)		51.20(7.20)	51.60(6.99)	50.17(7.63)	<0.01
Age categories	Under 45 years old	386(17.91)	256(16.44)	130(21.74)	<0.01
	45-54 years old	924(42.88)	649(41.68)	275(45.99)	
	55-64 years old	845(39.21)	652(41.88)	193(32.27)	
Marital status	Not married	751(34.85)	436(29.95)	315(57.17)	<0.01
	Married	1256(58.28)	1020(70.05)	236(42.83)	
Rural/Urban status	Urban	1634(75.82)	1232(79.13)	402(67.22)	<0.01
	Rural	521(24.18)	325(20.87)	196(32.78)	
Year of diagnosis	2002-2004	611(28.35)	452(29.03)	159(26.59)	0.02
	2005-2007	693(32.16)	518(33.27)	175(29.26)	
	2008-2010	851(39.49)	587(37.70)	264(44.15)	
Hormone receptor status	Positive	926(42.97)	709(81.03)	217(68.89)	<0.01
	Negative	264(12.25)	166(18.97)	98(31.11)	
Stage at Diagnosis	In-situ	422(21.72)	299(19.34)	123(20.78)	0.68
	Local	1013(47.01)	741(47.93)	272(45.95)	
	Regional	657(30.49)	470(30.40)	187(31.59)	
	Distant	46(2.13)	36(2.33)	10(1.69)	
Cancer grade	I	392(18.19)	300(21.29)	92(16.76)	<0.01
	II	785(36.43)	608(43.15)	177(32.24)	
	III	749(34.76)	479(34.00)	270(49.18)	
	IV	32(1.48)	22(1.56)	10(1.82)	

Best Chance Network	Yes	119(5.52)	60(3.85)	59(9.87)	<0.01
	No	2036(94.48)	1497(96.15)	539(90.13)	
Insurance provider	1	1640(76.10)	1285(82.34)	358(59.87)	<0.01
	2	515(23.90)	275(17.66)	240(40.13)	
Average distance to AHT provider (miles)		7.25 \pm 17.00	7.19 \pm 18.09	7.44 \pm 13.40	0.79
Average distance to Surgery provider (miles)		19.89 \pm 23.54	19.99 \pm 25.03	19.60 \pm 19.11	0.72
Average distance to Radiation provider (miles)		18.64 \pm 18.54	18.19 \pm 18.30	19.75 \pm 19.11	0.17
Average distance to Chemotherapy provider (miles)		20.55 \pm 20.68	19.69 \pm 20.27	22.58 \pm 21.48	0.03

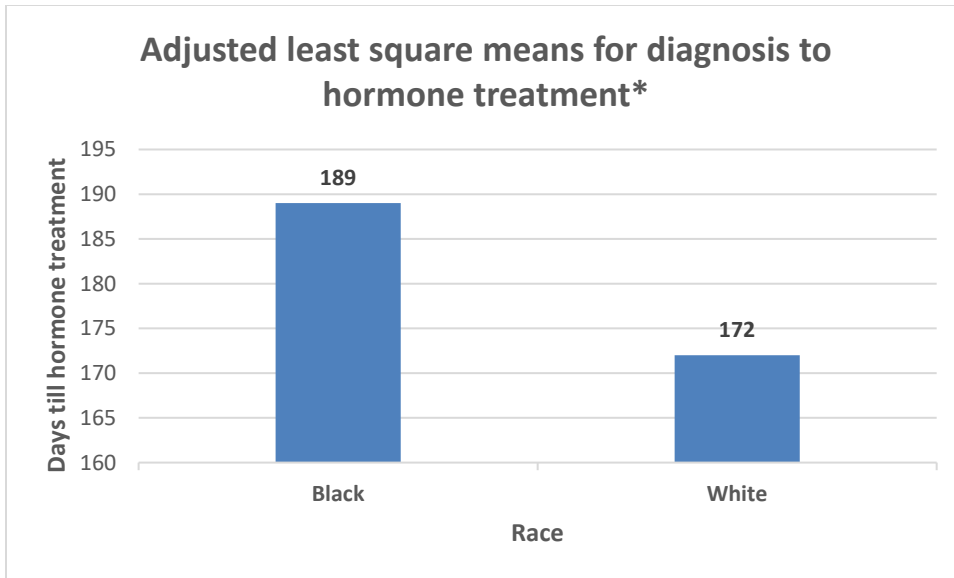


Figure 4.1: Adjusted least square means for diagnosis to hormone treatment showing increase of 17 days among blacks compared to whites

* $p < 0.01$ and Adjusted for age at diagnosis, diagnosis year, hormone-receptor status, stage, grade urban status and distance to providers.

Table 4.2 Diagnosis-to-hormone treatment times stratified by BCN, marital status*, early/late surgery and insurance provider**

	LSM (95% C.I.)	LSM (95% C.I.)
	Married (Yes)	Married (No)
White	190.08	166.42
Black	210.11	213.01
Black-White	20.03	46.59
% Increase	10.54	28.00
p-value	0.19	<0.01
	BCN (Yes)	BCN (No)
White	173.63	153.78
Black	175.85	186.24
Black-White	2.22	32.46
% Increase	1.28	21.11
p-value	0.93	<0.01
	Surgery 30 (Early)	Surgery 30 (Late)
White	154.39	169.94
Black	178.76	211.47
Black-White	24.37	41.53
% Increase	15.78	24.43
p-value	0.07	0.01
	Surgery 60 (Early)	Surgery 60 (Late)
White	165.53	158.91
Black	187.91	221.75
Black-White	22.38	62.84
% Increase	13.52	39.54
p-value	0.06	0.01
	Insurance provider 1	Insurance provider 2
White	160.23	188.27
Black	206.09	189.20
Black-White	45.87	0.93
% Increase	28.63	0.49
p-value	<0.01	0.96

*All models adjusted for age at diagnosis, diagnosis year, hormone-receptor status, stage, grade urban status and distance to providers.

**Best Chance Network

Table 4.3 Racial disparities among breast cancer patients and the odds of late receipt of surgery stratified by marital status, urban status and distance

Characteristic	Race	Total	Early receipt (<22 days) 918(44.98%)	Late receipt (≥22 days) 1123(55.02%)	Crude OR	Adjusted OR*
Overall			No (%)	No (%)	OR (CI)	OR (CI)
	White	1470(72.02)	700(47.62)	770(52.38)	Reference	Reference
	Black	571(27.98)	218(38.18)	353(61.82)	1.47(1.21-1.79)	1.59(1.28-1.98)
Married						
Yes	White	965(80.89)	463(47.98)	502(52.02)	Reference	Reference
	Black	228(19.11)	100(43.86)	128(56.14)	1.18(0.88-1.58)	1.39(1.00-1.92)
No	White	409(57.93)	187(45.72)	222(54.28)	Reference	Reference
	Black	297(42.07)	96(32.32)	201(67.68)	1.76(1.29-2.41)	1.96(1.38-2.79)
Urban status						
Rural	White	308(62.47)	160(51.95)	148(48.05)	Reference	Reference
	Black	185(37.53)	67(36.22)	118(63.78)	1.90(1.31-2.77)	2.40(1.55-3.73)
Urban	White	1162(75.06)	540(46.47)	622(53.53)	Reference	Reference
	Black	386(24.94)	151(39.12)	235(60.88)	1.35(1.07-1.71)	1.40(1.08-1.82)
Distance						
≤10miles	White	526(70.79)	283(53.80)	243(46.20)	Reference	Reference
	Black	217(29.21)	87(40.09)	130(59.91)	1.74(1.26-2.40)	1.89(1.32-2.71)
>10 miles	White	831(72.89)	385(46.33)	446(53.67)	Reference	Reference
	Black	309(27.11)	120(38.83)	189(61.17)	1.36(1.04-1.77)	1.49(1.12-2.01)

*Models adjusted for age, diagnosis year, hormone-receptor status, stage, grade and being in best chance network (BCN), definitive surgery type and insurance provider.

Table 4.4 Racial disparities among breast cancer patients and the odds of late receipt of post-surgery radiation stratified by age, hormone receptor status, best chance network, and insurance provider.

Characteristic	Race	Total	Early receipt (<60 days) 675(48.67%)	Late receipt (≥ 60 days) 712(51.33%)	Crude OR	Adjusted OR*
Overall			No (%)	No (%)	OR (CI)	OR (CI)
	White	995(71.74)	508(51.06)	487(48.94)	Reference	Reference
	Black	392(28.26)	167(42.60)	225(57.40)	1.41(1.11-1.78)	1.17(0.86-1.56)
Age						
<45	White	171(66.80)	82(47.95)	89(52.05)	Reference	Reference
	Black	85(33.20)	25(29.41)	60(70.59)	2.21(1.27-3.85)	2.18(0.99-4.80)
45-54	White	412(69.95)	192(46.60)	220(53.40)	Reference	Reference
	Black	177(30.05)	76(42.94)	101(57.06)	1.16(0.81-1.65)	0.95(0.59-1.53)
55-64	White	412(76.01)	234(56.80)	178(43.20)	Reference	Reference
	Black	130(23.99)	66(50.77)	64(49.23)	1.27(0.86-1.89)	0.93(0.56-1.57)
Hormone Receptor Status						
Positive	White	464(76.32)	246(53.02)	218(46.98)	Reference	Reference
	Black	144(23.68)	57(39.58)	87(60.42)	1.72(1.18-2.52)	1.44(0.86-2.39)
Negative	White	110(60.44)	32(29.09)	78(70.91)	Reference	Reference
	Black	72(39.56)	23(31.94)	49(68.06)	0.87(0.46-1.66)	0.30(0.10-0.93)
Insurance						

provider						
1	White	830(77.28)	441(53.13)	389(46.87)	Reference	Reference
	Black	244(22.72)	106(43.44)	138(56.56)	1.48(1.10-1.97)	1.29(0.88-1.89)
2	White	165(52.72)	67(52.34)	98(59.39)	Reference	Reference
	Black	148(47.28)	61(41.22)	87(58.78)	0.98(0.62-1.53)	0.84(0.47-1.53)

* Models adjusted for marital status, urban status, diagnosis year, stage, grade, distance, definitive surgery type and receipt of early/late surgery.

Table 4.5 Racial disparities among breast cancer patients and the odds of late receipt of chemotherapy stratified by urban status and late surgery

Characteristic	Race	Total 1134(100 %)	Early receipt (<60 days) 556(51.44%)	Late receipt (≥ 60 days) 578(50.97%)	Crude OR	Adjusted OR*
Overall			No (%)	No (%)	OR (CI)	OR (CI)
	White	797(70.28)	410(51.44)	387(48.56)	Reference	Reference
	Black	337(29.72)	146(43.32)	191(56.68)	1.39(1.07-1.79)	1.00(0.68-1.48)
Rural/ Urban						
Rural	White	164(59.42)	94(57.32)	70(42.68)	Reference	Reference
	Black	112(40.58)	39(34.82)	73(65.18)	2.51(1.53-4.13)	1.93(0.81-4.60)
Urban	White	633(73.78)	316(49.92)	317(50.08)	Reference	Reference
	Black	225(26.22)	107(47.56)	118(52.44)	1.10(0.81-1.49)	0.76(0.48-1.21)
Surgery						
Early	White	329(73.60)	2012(61.40)	127(38.60)	Reference	Reference
	Black	118(26.40)	74(62.71)	44(37.29)	0.95(0.61-1.46)	0.84(0.43-1.62)
Late	White	433(67.87)	195(45.03)	238(54.97)	Reference	Reference
	Black	205(32.13)	68(33.17)	137(66.83)	1.65(1.17-2.34)	0.89(0.52-1.52)

* Models adjusted for age, marital status, diagnosis year, stage, grade, distance, insurance provider, and definitive surgery type.

CHAPTER 5

ASSESSMENT OF RACIAL DISPARITIES IN MORTALITY AMONG BLACKS AND WHITES DIAGNOSED WITH BREAST CANCER IN SOUTH CAROLINA

Introduction

Statistics over the past 20 years in the United States have shown higher mortality rates among Blacks with breast cancer (BrCA) compared to Whites despite lower incidence of BrCA among Blacks.⁽¹⁻⁴⁾ The need to study disparities on survival among BrCA patients in SC is particularly important because Black-White disparity in BrCA mortality is of a higher magnitude in SC;^(30, 40, 41) mortality among White BrCA patients is 7% lower in SC compared to the national average and is 29% higher among Blacks in SC.^(30, 40, 41) Also, in SC, mortality from BrCA amongst Blacks is greater than 60% than that of Whites.⁽⁵⁾ Studies also show that Blacks experience worse mortality outcomes after matching for known prognostic factors, and this finding has persisted over time.⁽⁴²⁻⁴⁵⁾

Factors that have been shown to influence BrCA survival are age, enrolment in best chance network, socioeconomic status, hormone receptor status, health insurance type, stage at diagnosis, type of surgery, complications of surgery, marital status and county of residence (whether rural or urban).^{(55, 65, 67, 71, 72, 74, 79, 105, 124, 128, 140, 142, 143, 145, 148-}

¹⁵¹⁾ This study will add to existing body of literature on racial disparities BrCA-specific survival (BSS),⁽⁵⁶⁾ and overall survival (OS).^(57, 58) Assessment of survival differences in this study by regions in SC has not been studied before. The aim of this study was to describe the breast cancer-specific and overall survival in SC, as well as by the four health regions and to assess the factors (confounders and effect modifiers) affecting survival among Black and Whites in SC overall. We hypothesize that treatment and mortality outcomes will be worse for Blacks who live in Pee Dee, which are characterized by lower socioeconomic status, and will be better in Midlands and Low Country because of the major hospital systems available in these regions.

Methods

Data Source

This was a retrospective cohort study (2002 to 2010) that included data on all BrCA patients derived from linked files from the SCCCR and Office of Revenue and Fiscal Affairs (which maintains the administrative medical claims data for a private payor plan and Medicaid). The study was exempt from IRB review by the University of South Carolina IRB. All newly diagnosed cases of cancers are collected by SCCCR, which is a population-based system in SC. Data in the SCCCR include information on demographics, diagnosis date, cancer location and histology, treatment and overall survival.⁽³⁸⁾ All incident cancer cases are required by law to be reported to SCCCR, a resource established with funding from an award from the National Program of Cancer Registries (NPCR) in 1994.

The SCCCR from which we derived the data for this analysis has a history of receiving the highest/gold rating for data completeness (>94%), timeliness and data quality from the North American Association of Central Cancer Registries and NPCR. SCCCR is a member of the CDC National Interstate Data Exchange System (N-IDEAS), such that any member state may share resident incident cases with others to ensure the completeness of incident cancer data. A cohort of 2,155 patients from the SCCCR with a diagnosis of female breast cancer from 2002 to 2010 was created. This cohort was linked to the same patients in the SC State Employee Health Plan and Medicaid datasets. The resulting combined dataset were used to conduct all analyses.

Data Linkage and Security

Linkages were made with 3 personal identifiers: name, date of birth and social security number. These linkages were performed by RFA in partnership with SCCCR. Because of data security issues, only the final de-identified dataset was released to study personnel and investigators for analysis. The key to the de-identified dataset was retained by RFA in the event that further data clarifications were needed from the primary record. Once the de-identified data were received, the study data manager performed routine outlier and logic checks. Any improbable values were verified with RFA or SCCCR and rectified where possible. To create an analytic dataset, we utilized datasets from the RFA (Medicaid and State Health Plan), BCN and SCCCR to create an extensive look at breast cancer treatment in South Carolina for Black and White women. Data acquisitions were linked through the aforementioned departments by the RFA, and only a study participant number was assigned to each person for analysis by investigators. Because the final dataset was completely de-identified, the investigators have no linkages to the original

identifiable patient contact information and will be referred to via a study participant number only.

Variables

Exposure Variable: The main exposure variable was race of the BrCA cases, dichotomized as Black or White. Variables that were considered as covariates or effect modifiers were age, marital status, county of residence, year of diagnosis, hormone receptor status, enrollment in BCN (dichotomized as yes or no), stage of BrCA at diagnosis and grade of BrCA at diagnosis.

Outcome Variables: *Overall and breast cancer mortality.* We utilized vital status, total survival time, and BrCA cause of death (yes/no) for this investigation. From cause of death information, we were able to examine both all-cause/overall mortality, as well as BrCA-specific mortality.

Exploratory Data Analysis: Kaplan-Meier survival curves were used to explore 5-year and 12-year survival for BrCA-specific and all-cause survival at the state and regional levels. This was also stratified by race at the state and regional levels. Log rank test was used to assess the Kaplan-Meier plot with respect to race which was the main exposure. To test for adequacy of proportional hazard (PH) model, we graphically inspected whether the log-log survival (lls) curve were parallel with respect to the exposure of interest (race). The PH model was satisfied as the curves were parallel. Each exposure variable was tested utilizing the Schoenfeld Residual to ascertain the adequacy of using PH model. The PH model was satisfied for all variables tested.

Assessment of interactions: In assessing the relationship between race and mortality, interactions were assessed. Statistically significant interactions were noted between race and marital status; race and urbanicity; race and region; race and BCN. The analyses that assessed factors that influence disparity in mortality were therefore stratified by these four variables.

Fitting the best model in each stratum: In each stratum, the relationships between race and mortality (breast-cancer specific and all-cause) were assessed by fitting the best Cox PH model through backward elimination starting with all potential covariates like age, year of diagnosis, hormone receptor status, enrollment in BCN (dichotomized as yes or no), stage of BrCA at diagnosis and grade of BrCA at diagnosis.

Results

Descriptive statistics for this study sample are shown in Table 1. Overall, there were 2155 cases of breast cancer patients of which the majority were Whites (1557, 72.25%). In bivariate analyses, there were significant differences between Blacks and Whites in age, rural/urban status, year of diagnosis, hormone receptor status, cancer grade, cancer stage and insurance provider. Blacks were more likely to be in age group 45-54 (45.99%) while Whites were more likely to be in age group 55-64 years (41.88%). Blacks were more likely to be unmarried (57.17%) compared to Whites (29.95%). The proportion of Whites that live in urban area (79.13% vs 67.22%) and have hormone receptor positive cancer (81.03% vs 68.89%) is higher among Whites compared to Blacks. More Blacks were participants in BCN compared to Whites (9.87% compared with 3.85%).

Figure 1 presents the Kaplan Meier plots of 12-year BrCA-specific mortality among Blacks and Whites in the state of SC and in Low Country region. There was statistically significant difference between Blacks and Whites in the state overall; however, among the 4 health regions, only the Low Country region had statistically significant difference with mortality higher among Blacks. This difference is seen as early as 3 years and it continues to widen till 12 years. Figure 2 is the all-cause mortality variant of Figure 1 and the findings are similar to that of Figure 1.

Table 2 shows the 5- and 12- year survival proportion for BrCA-specific and all-cause mortality among Blacks and Whites in the entire state of SC and also by the 4 health regions in SC. Table 2 shows that both the 12- year BrCA specific survival (91.3%) and the 12-year overall survival (89.3%) were highest in Low Country region, however, the black-white disparity was also higher in this region. As seen in Figure 1 and 2, Table 1 also shows that there is significant increase in mortality among Blacks relative to Whites in the data that examined the state of SC and in the Low Country region of the state.

The crude hazard ratio of mortality among Blacks compared with Whites was 1.42 (1.03, 1.95) for overall survival and 1.49 (1.04, 2.14) for BrCA specific survival (data not shown). Table 3 presents the Cox proportional hazard models. Multivariable Cox proportional hazard that adjusted for cancer stage showed that the hazard ratio of mortality was 3.45 (1.64,7.25) among Black women who lived in Low Country region of the state compared with White women who lived in Low Country region of the state when all-cause mortality was examined. A similar hazard ratio of mortality of 3.79 (1.68, 8.58) was seen among Black women who lived in Low Country region of the state

compared with White who lived in same region when BrCA-specific mortality was examined. In the other three regions of the state (Midlands, Pee Dee and Upstate); there were no statistically significant differences in hazard ratio that compared Blacks with Whites. Multivariable Cox proportional hazard that adjusted for cancer stage and grade showed that the hazard ratio of mortality was 1.53 (1.04,2.26) among Black women who lived in urban areas compared with White women who lived in urban areas for all-cause mortality.

Discussion

The Kaplan Meier model found that there was a statistically significant difference between Blacks and Whites in the state of SC overall, however, among the 4 health regions, only the Low Country region had statistically significant difference with mortality higher among Blacks. This difference is seen as early as 3 years and it continues to widen till 12 years. Also, in the Kaplan Meier model, the Low Country region had higher BrCA survival than the other three regions, but it also demonstrated the widest racial disparity. In Cox Proportional multivariable model, we also showed that hazard ratio of mortality was 3.45(1.64,7.25) among Black women who lived in Low Country region of the state compared with White women who lived in Low Country region of the state when all-cause mortality was examined; and 3.79 (1.68, 8.58) was seen among Black women who lived in Low Country region of the state compared with White who lived in same region when BrCA-specific mortality was examined. Multivariable Cox proportional hazard that adjusted for cancer stage and grade showed that the hazard ratio of mortality was 1.53(1.04,2.26) among Black women who lived in urban areas compared with White women who lived in urban areas for all-cause mortality.

The crude hazard ratio of mortality among Blacks compared with Whites was 1.42 (1.03, 1.95) for overall survival and 1.49 (1.04, 2.14) for BrCA specific survival which represents 40% excess risk for overall survival and 50% excess risk for BrCA specific survival. However, this finding was no longer significant on multivariable model which makes our finding different from previous similar studies in SC that found that there is a 60% higher risk of Black women dying from BrCA compared to White women.

These previous studies showed that although the Black-White disparity in BrCA mortality is seen both at the national level and in SC specifically, the disparity is of a higher magnitude in SC (5, 30, 40, 41, 156); mortality among White BrCA patients is 7% lower in SC compared to the national average and is 29% higher among Blacks in SC (30, 40, 41). One of the possible reasons for these differences is because some of the studies that assessed the mortality differences in SC utilized age adjusted mortality while we utilized the Cox Proportional hazard model with adjustments. For example, a previous study that found that a paradoxical relationship of a lower incidence of breast cancer but higher death rates among Blacks considered the age-adjusted rate. (156) Our study therefore underscores the additional importance of going a step further after utilizing age-adjusted data to also modelling using statistical means to assess the relationship between mortality and race among BrCA patients.

We found from the Kaplan Meier model that the 5-year, and 12-year survival was higher among Whites in the state of SC overall but when this was stratified by region, only the Low Country region demonstrated a wide disparity while there was no significant difference between Blacks and Whites in the other three regions. This finding was additionally supported by the multivariable adjusted hazard ratio for mortality which

showed that Blacks in the Low Country region had mortality hazard ratio of 3.45 (1.64, 7.25) after adjusting for cancer stage, cancer grade and age. This shows that the racial disparities seen in BrCA mortality seen in SC is being driven mainly by the disparity seen in Low Country region of the state. What is interesting though, is that using the Kaplan Meier model, the Low Country had the highest 12-year survival for both all-cause and BrCA specific mortality (91.3% and 89.3% respectively). It therefore appears that overall (when Blacks and Whites are combined), Low Country has the best mortality outcome related to the other three regions but when Black-White disparity is considered, the Low Country has the highest racial disparity.

This finding may be helpful to help inform policy direction in the SC's state BCN program which is an early detection program for breast and cervical cancer (41, 141). Women that are eligible for this program are those that are aged 47-64 years, residents of SC, underserved/underinsured or do not have insurance and are of low income (less than 200% of the Federal poverty level). This program provides free breast and cervical cancer screening and started because SC has one of the highest rates of uninsured women the United States (40, 41, 141). Recruitment into the BCN program is usually through active search by federally qualified health centers, the South Atlantic Division, media outlets and through outreaches carried out by the American Cancer Society. (41, 141). Our finding may help the administrators of the BCN program to plan and focus efforts to reduce racial disparities to certain regions of the state or implement special programs for those regions.

Obesity rate may be one of the factors affecting the racial disparities in the Low Country region of SC. In SC, it has been hypothesized that comorbid illnesses and

obesity could be the driver of cancer racial disparity. (157) Obesity and comorbid illnesses affect Blacks in SC at a rate that is above the national average. (157, 158) In 2018 report, SC has the 10th highest adult obesity rate in the US, this is up from being the 13th highest in 2016. Comparing these figures to that of 2000 and 1999 (21.1% and 12% respectively), the weight gain problem appears to be persistently on the rise in SC. (157, 158) A previous study as shown that severe obesity and high waist-to-hip ratio among

Blacks have also been found to contribute to racial differences in stage at BrCA diagnosis, as Blacks had a higher likelihood of severe obesity and being in the highest tertile of waist-to-hip ratio (64). SC diabetes and hypertension rate are currently 5th highest and 8th highest (13.4% and 38.1% respectively) in the US and physical activity ranking 17%. When the obesity rate in SC is broken down by Black-White race, it is 42.1% (ranking 9th) in Blacks while it is 29.6% (ranking 25th) in Whites. Specifically in Charleston, the largest city in the Low Country, the overweight or obese rate is 73.1% among Blacks and 63.4% among Whites. (159) When the obesity rate by county was ranked, 56% (five out of nine) of counties that had the highest obesity rate in SC (obesity rate \geq 40%) were in Low Country region [Allendale, Bamberg, Colleton, Hampton and Orangeburg]. (158)

The regional sub-population of the Gullahs may also be one of the factors affecting the racial disparities in the Low Country region of SC. The Gullahs are a unique Black sub-population that live and reside in the farming and the fishing communities along SC's coastal areas. (157) The Gullah community are geographically isolated and previous studies have shown that they experienced limited access to health care and are at a higher risk of cardiometabolic risk factors for diabetes mellitus. (160, 161) The

Gullah's limited access to care (though for diabetes mellitus) may also have affected their receipt of care for BrCA as shown by other reports that Blacks also have various barriers to accessing care. Blacks have been shown to consistently receive lower-than-recommended BrCA care when compared with their White counterparts (21, 25, 43, 61, 73, 78). This includes lower-than-recommended rates of radiation after surgical treatment for BrCA (25, 43, 61, 78). Blacks have also been shown to be 30-40% more likely to receive BrCA treatments that are not in line with guidelines across all BrCA subtypes (79). Previous studies have also shown that there is a tendency among Blacks to not receive preventative services such as early screening mammograms (77).

Socioeconomic status (SES) has been identified as one of the main drivers of racial disparities in BrCA mortality, as women in low socioeconomic levels tend to present with more advanced-stage BrCA, which usually has poorer prognosis (71, 80). Specifically, in Charleston, the median income in 2015 for a white family in Charleston—North Charleston was more than double for black families, \$64,553 compared to \$29,799. That means more than 15,000 black families in Charleston and North Charleston were living on the edge of the poverty guideline—\$24,250. Charleston County has is of the worst counties in the United States in helping poor children up the income ladder. It ranks 242nd out of 2,478 counties, better than only about 10% of counties nationwide. (159) Generally, the five-year survival rate is worse among population subgroups with lower SES, which are usually comprised of a large proportion of Blacks (71, 81). Whereas about 12% of Whites live below the poverty level, this proportion is 26% among Blacks (71, 82). Additionally, when median income by county was ranked, 33 % (five out of 15) of counties that had the lowest median income in SC (median household income \leq

35,558) were in Low Country region [Allendale, Bamberg, Colleton, Hampton and Orangeburg]. (158) These five counties were the same counties with the higher obesity rate. (158)

This study added to existing body of literature on racial disparities on BrCA-specific survival (BSS), (56) and overall survival (OS) (57, 58). To our knowledge, this is the first cancer disparity study in SC that has conducted a regional analysis thereby showing that the Low Country region appears to be the driver of the racial disparities seen in BrCA patients in SC. One weakness of this study is that we did not assess the Hispanic population because the BrCA patients had very low sub-population in SC. Additionally, our study was limited in the number of other biological, patient-, physician-, and healthcare-system-related factors that could have been assessed to further study our observations especially in the Low Country region.

In conclusion, mortality was higher among Blacks who lived in the Low Country region of the state and among Blacks who lived in urban areas. Although the Low Country region had the highest 12-year survival among a combination of Whites and Black population, relative to other three health regions, it demonstrated the highest Black-White racial disparity relative to the other three regions. Despite the awareness and funding dedicated to closing the racial gap in cancer therapy, it is discouraging to note that racial disparities persist in BrCA mortality (60, 61). Navigation programs and other available programs aimed at reducing racial disparities may benefit from these finding by committing more resources that are culturally acceptable to the Low Country region of SC. Considering that Low Country seemed to have the best mortality outcome (when combined data is used) but the worse Black-White disparity, the Low Country region

may benefit from specific community-oriented interventions similar to the community COMPASS project (157) that has the potential to close this gap. To reduce racial disparity gap in survival in SC, Black breast cancer patients that live in Low Country region and those that live in urban areas may benefit from more intense navigation efforts directed at early detection and linkage to receipt of breast cancer treatments. Future studies are also required to identify the potential, biological, patient-, physician-, and healthcare-system-related factors underlying our observations and optimize cancer care among Blacks in SC particularly in the Low Country region. Additionally, the state of SC will benefit from future studies to assess the regional disparities in other common cancers to identify if this trend seen in the Low Country specific to BrCA or other cancers in order to inform future implementation regional appropriate policies that may help to close this gap.

Table 5.1 Summary of patients' characteristics by race

		N (%)	N (%)	N (%)	
Characteristic		Total (N=2155)	White N=1557 (72.25)	Black N=598 (27.75)	P
Age (mean±SD)		51.20(7.20)	51.60(6.99)	50.17(7.63)	<0.01
Age categories	Under 45 years old	386(17.91)	256(16.44)	130(21.74)	<0.01
	45-54 years old	924(42.88)	649(41.68)	275(45.99)	
	55-64 years old	845(39.21)	652(41.88)	193(32.27)	
Marital status	Not married	751(34.85)	436(29.95)	315(57.17)	<0.01
	Married	1256(58.28)	1020(70.05)	236(42.83)	
Rural/Urban status	Urban	1634(75.82)	1232(79.13)	402(67.22)	<0.01
	Rural	521(24.18)	325(20.87)	196(32.78)	
Year of diagnosis	2002-2004	611(28.35)	452(29.03)	159(26.59)	0.02
	2005-2007	693(32.16)	518(33.27)	175(29.26)	
	2008-2010	851(39.49)	587(37.70)	264(44.15)	
Hormone receptor status (both hormones)	Positive	926(42.97)	709(81.03)	217(68.89)	<0.01
	Negative	264(12.25)	166(18.97)	98(31.11)	
Stage at Diagnosis	In-situ	422(21.72)	299(19.34)	123(20.78)	0.68

	Local	1013(47.01)	741(47.93)	272(45.95)	
	Regional	657(30.49)	470(30.40)	187(31.59)	
	Distant	46(2.13)	36(2.33)	10(1.69)	
Cancer grade	I	392(18.19)	300(21.29)	92(16.76)	<0.01
	II	785(36.43)	608(43.15)	177(32.24)	
	III	749(34.76)	479(34.00)	270(49.18)	
	IV	32(1.48)	22(1.56)	10(1.82)	
Best Chance Network	Yes	119(5.52)	60(3.85)	59(9.87)	<0.01
	No	2036(94.48)	1497(96.15)	539(90.13)	

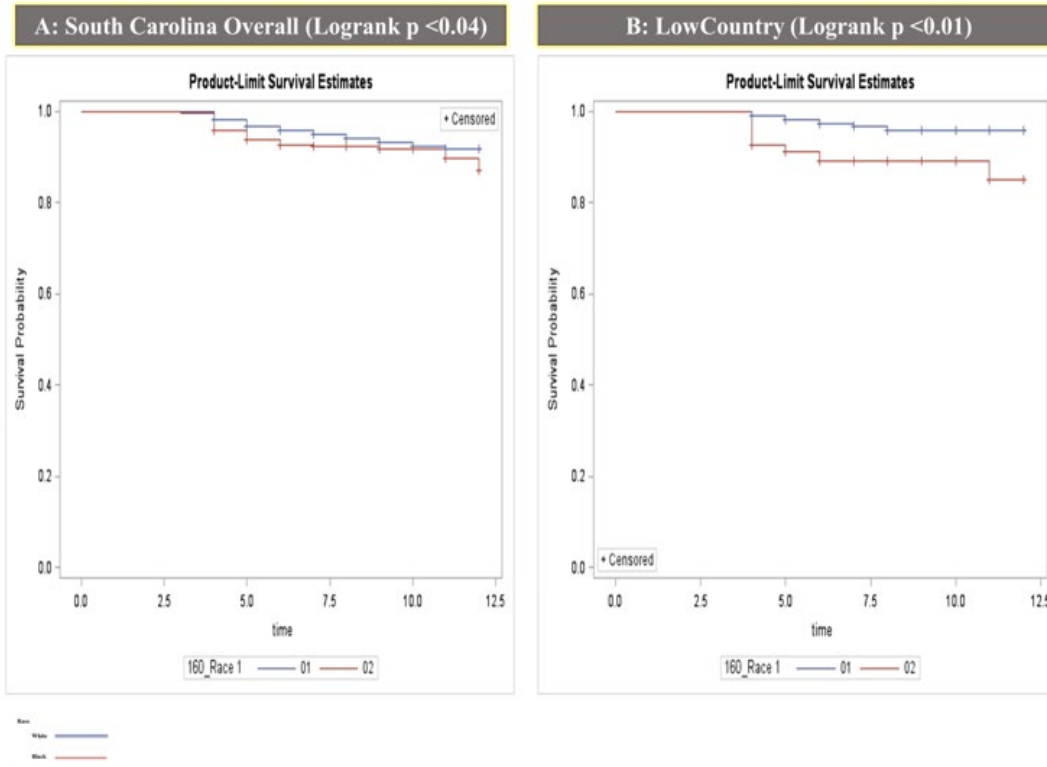


Figure 5.1: Kaplan Meier curves for the association between race and 12-year Breast Cancer Specific Mortality in SC

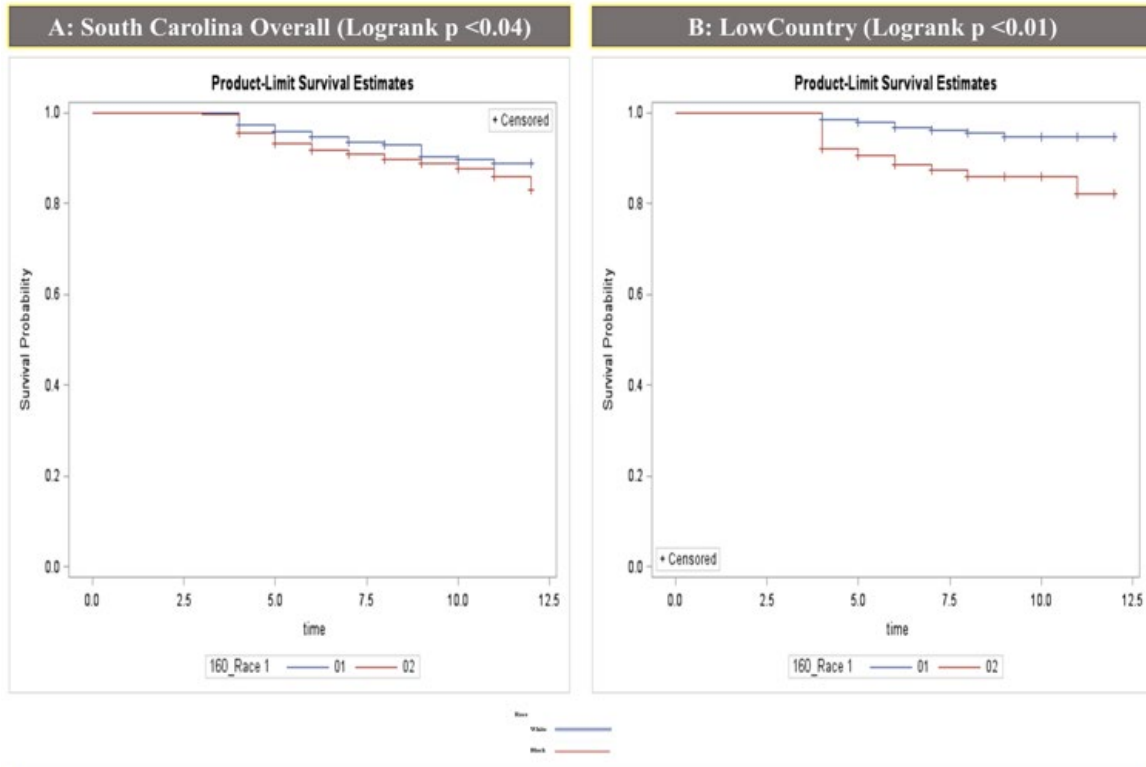


Figure 5.2 Kaplan Meier curves for the association between race and 12-year All-Cause Mortality in SC

Table 5.2: 5-year and 12-year survival by region and by race in South Carolina

		BrCA-specific survival		Overall survival	
		5YST (%)	12YST (%)	5YST (%)	12YST (%)
South Carolina	Overall	95.6	89.3	94.8	85.8
	Black	93.3	85.5	92.8	81.2
	White	96.5	90.1	95.7	87.3
	p-value		0.03		0.03
Midlands region	Overall	95.6	89.3	94.8	85.3
	Black	95.0	90.0	94.3	86.6
	White	95.8	89.0	94.9	84.9
	p-value		0.70		0.46
Low Country Region	Overall	95.5	91.3	95.0	89.3
	Black	90.3	81.9	89.7	78.8
	White	98.0	95.6	97.7	94.3
	p-value		<0.01		<0.01
Pee Dee	Overall	95.2	82.9	93.7	78.5
	Black	94.7	80.1	95.0	75.7
	White	95.5	87.4	93.4	82.7
	p-value		0.67		0.76
Upstate	Overall	96.1	90.7	95.8	87.5
	Black	92.1	92.1	92.1	84.1
	White	96.7	90.7	96.1	88.1
	p-value		0.43		0.28

Table 5.3: Table HR and 95% CI for the associations between predictors and all-cause and BrCA specific mortality by race in SC state overall

Character istic	Race	Death	Adjusted HR** Overall survival	Adjusted HR** BrCA-specific survival
Overall		No (%)	HR (CI)	HR (CI)
	White	112(7.19)	1.00	1.00
	Black	57(9.53)	1.28(0.92,1.77) ^a	1.30(0.90,1.88) ^a
Married				
Yes	White	70(6.86)	1.00	1.00
	Black	11(4.66)	0.78(0.41,1.47) ^b	0.71(0.35,1.46) ^a
No	White	36(8.26)	1.00	1.00
	Black	41(13.02)	1.53(0.97,2.42) ^a	1.78(1.06,3.01) ^c
Urban				
Yes	White	80(6.49)	1.00	1.00
	Black	39(9.70)	1.53(1.04,2.26) ^a	1.53(0.98,2.41) ^a
No	White	32(9.85)	1.00	1.00
	Black	18(9.18)	0.91(0.51,1.62) ^c	0.81(0.42,1.55) ^c
Region				
Low Country	White	11(3.77)	1.00	1.00
	Black	19(12.70)	3.45(1.64,7.25) ^c	3.79(1.68,8.58)
Midlands	White	44(9.02)	1.00	1.00
	Black	12(6.59)	0.68(0.35,1.31) ^a	0.72(0.35,1.51) ^a
Pee Dee	White	24(9.23)	1.00	1.00
	Black	18(10.29)	0.99(0.53,1.86) ^d	0.94(0.44,1.98) ^f
Upstate	White	33(6.38)	1.00	1.00
	Black	8(8.99)	1.43(0.66,3.10) ^c	1.32(0.54,3.21)
BCN				
Yes	White	2(3.33)	1.00	1.00
	Black	11(18.64)	1.43(0.66,3.10) ^c	1.32(0.54,3.21) ^c
No	White	110(7.35)	1.00	1.00
	Black	46(8.53)	1.22(0.86,1.72) ^a	1.14(0.77,1.70) ^a
Insurance				
1	White	65(5.07)	1.00	1.00
	Black	21(5.87)	1.09(0.66,1.80) ^a	1.06(0.61,1.85) ^a
2*	White	47(17.09)	1.00	1.00
	Black	36(15.00)	0.89(0.57,1.40) ^g	0.83(0.49,1.39) ^a

^aAdjusted for stage and grade. ^bAdjusted for stage and age.

^cAdjusted for stage. ^dAdjusted for stage, grade and age.

^eCrude HR reported because no additional variable met entry into the model for adjustment.

^fAdjusted for age and grade

^gAdjusted for age, stage and diagnosis year.

CHAPTER 6

GEOSPATIAL ASSESSMENT OF RACIAL BREAST CANCER DISPARITY IN MORTALITY-TO-INCIDENCE RATIO AND SURVIVAL ANALYSES CORRELATION IN SOUTH CAROLINA.

Introduction

The epidemiologic use of the mortality-to-incidence ratio (MIR) in cancer research is gaining significance and is increasingly used (5, 10-14, 38) as a unique way to quantify cancer disparities based on race (5, 10). The MIR is an important indicator that offers additional information beyond what is represented through the individual incidence and mortality rate measures. (5) The MIR also serves as a population-based approximation of fatality ($1/\text{survival}$) given incidence by stabilizing the incidence and mortality differences across cancer sites and racial groups (5, 10). Recommendations have been made for cancer surveillance programs to use MIRs to monitor disparities across racial/ethnic groups and geographic regions (5, 10-14, 38) as a proxy for survival, but there is paucity of studies that assessed the effectiveness of MIR as a proxy for survival among BrCA patients, especially in South Carolina where there is marked Black-White disparity. (38)

Previous studies have utilized the MIR as a surveillance tool and shown that SC exhibits more extreme racial differences in cancer incidence, mortality and MIR than other states or the nation. (30-38) Additionally, examining the MIR helped to highlight health regions where this disparity is highest. (38) A major drawback of the MIR, however, is that there is no method to account for censoring and loss to follow up. Additionally, the MIR most likely counts the mortality from previous years while using incidence from the current year hence it is not a classic case fatality proportion. It is also not possible to adjust for covariates such as treatment, comorbidities or individual socioeconomic status in MIR analysis. Another weakness is that the relationship between the numerator (mortality) and the denominator (incidence) may not be direct because persons diagnosed with BrCa may not die of BrCa, and persons who die after the diagnosis of BrCa will survive for varying lengths of time, which the MIR cannot account for.

The limitations of the MIR described above make it difficult to compare results of MIR studies directly with those of survival studies. Survival studies are more complex, time-consuming and expensive and require more skills to carry out. Additionally, data needed to conduct survival analyses is not publicly available and date of diagnosis and death are protected data elements which most cancer registries will not release. Using MIR is less time-consuming, less expensive and requires fewer skills to carry out. (5) The potential utility of the MIR in cancer surveillance programs for monitoring disparities across racial/ethnic groups and geographic regions is substantial, as shown by previous studies. (5, 10, 12, 14, 38) It is therefore important to see how the MIR compares with survival studies in identifying racial disparities and in ranking health regions for the

purpose of surveillance. To our knowledge, this is the first study that seeks to directly compute MIR by health regions and compare this ranking with a ranking produced by median survival time to further substantiate the usefulness of the MIR in resource-poor settings and in quick decision making to identify areas that need urgent interventions.

This study added further to the usefulness of MIR that was found from a sensitivity analysis described previously by Sunkara et al. (152) that examined the effect of moving across different “denominator years” to vary with the alignment of the average incidence-to-mortality time interval. The sensitivity analysis used all combinations of sex and race for cancers involving all anatomic sites. It was shown that the lines describing the MIR remained parallel, with the rates generally remaining stable over time across eight different 5-year periods beginning in 1996. This analysis was performed using incidence data from the SC Central Cancer Registry (SCCCR) (152).

The aim of this work is to assess the validity of MIR as a proxy for survival and geospatially investigate racial disparity among BrCA patients. This was achieved by comparing the MIR methodology with survival methodology in assessing racial BrCA disparities across the four health regions in SC. We hypothesize that the MIR will be a valid analyses compared with survival analyses by region.

Methods

Data for survival analyses

Data for survival analyses is from a retrospective cohort study (2002 to 2010) that included data on all BrCA patients derived from linked files from the SCCCR and Office of Revenue and Fiscal Affairs (which maintains the administrative medical claims data

for the South Carolina Public Employee Benefits plan and Medicaid). The study was exempt from IRB review by the University of South Carolina IRB because it was a deidentified data. All newly diagnosed cases of cancers are collected by SCCCCR, which is a population-based system in SC. Data in the SCCCCR include information on demographics, diagnosis date, cancer location and histology, treatment and overall survival. (38)

The data was linked with data from SC Revenue and Fiscal Affairs Office (RFA) which is an independent agency that houses administrative claims data from both SC State Employee Health Plan and SC Medicaid plan members. The RFA developed a series of algorithms using various combinations of personal identifiers to create its own unique identifier, enabling statistical staff to “link across” multiple providers and settings. Hence, it allows for linkages while protecting the confidentiality of the client. The SC Revenue and Fiscal Affairs Office and SC Central Cancer Registry frequently work together to complete data linkage requests for researchers in SC. All BrCA cases between the time period of 2002 to 2010 who met eligibility criteria (that could be ascertained from their files) were given to RFA. Then RFA matched to determine which cases linked and further met our eligibility criteria (that required claims data to ascertain). This resulted in the 2155 cases. This resulting combined dataset was used to conduct all analyses.

This cohort was linked to the same patients in the SC State Employee Health Plan and Medicaid datasets. The resulting combined dataset will be used to conduct all analyses. Linkages were made with 3 personal identifiers: name, date of birth and social security number. As per protocol, these linkages were performed by RFA in partnership

with SCCCR. Because of data security issues, only the final de-identified dataset was released to study personnel and investigators for analysis. The key to the de-identified dataset was retained by RFA in the event that further data clarifications are needed from the primary record. Once the de-identified data were received, the study data manager performed routine outlier and logic checks. Any improbable values were verified with RFA or SCCCR and rectified where possible.

To create an analytic dataset, we utilized datasets from the RFA (Medicaid and State Health Plan), BCN and SCCCR to create an extensive look at breast cancer treatment in South Carolina for Black and White women. Data acquisitions were linked through the aforementioned departments by the RFA, and only a study participant number was assigned to each person for analysis by investigators. Because the final dataset was completely de-identified, the investigators have no linkages to the original identifiable patient contact information and will be referred to via a study participant number only.

Data for the MIR

Data for the MIR were obtained from SC Central Cancer Registry (SCCCR) online query system which is in the SC Department of Health and Environmental Control (DHEC) Office of Public Health Statistics and Information Services. Aggregate data for the age-adjusted mortality and incidence rates were obtained from the SC DHEC. Data on breast cancer was used in computing the incidence and mortality rates for BrCA, All incident BrCA cases are required by law to be reported to SCCCR, a resource established with funding from an award from the National Program of Cancer Registries (NPCR) in 1994. Enabling legislation from the SC General Assembly was enacted in 1996. Data are

collected by SCCCR on all cancers, both *in-situ* and invasive, from hospitals, pathology laboratories, freestanding treatment centers and physician offices. The only exceptions are *in situ* forms of cervical cancer and invasive forms of basal and squamous cell skin cancers of non-genital sites.

The SCCCR from which we will derive the data for this analysis has a history of receiving the highest/gold rating for data completeness (>94%), timeliness and data quality from the North American Association of Central Cancer Registries and NPCR. SCCCR is a member of the CDC National Interstate Data Exchange System (N-IDEAS), such that any member state may share resident incident cases with others to ensure the completeness of incident cancer data. Additionally, there is geocoding of all cancer cases and cancer deaths in the state of SC.

Variables for survival analyses

For the Kaplan Meier analyses and Cox Proportional hazard analyses, the main predictor variable was race of the BrCA cases, dichotomized as Black or White. We utilized vital status, total survival time, and BrCA cause of death (yes/no) for this investigation. From cause of death information, we were able to examine both all-cause/overall mortality, as well as BrCA-specific mortality. For Cox Proportional analyses (to compute hazard ratio by region), additional variables that were considered as covariates or effect modifiers were age, marital status, county of residence, year of diagnosis, hormone receptor status, enrollment in BCN (dichotomized as yes or no), stage of BrCA at diagnosis and grade of BrCA at diagnosis.

Variables for MIR

Comparisons of MIRs across the four DHEC health regions (Upstate, Midlands, Low Country and Pee Dee) was carried out. The variables that were utilized to calculate the MIR were age-adjusted incidence and age-adjusted mortality. Variables that were used to stratify the MIR maps across the four health regions are race of the BrCa cases dichotomized as Black or White.

Analyses

Survival Analyses

Kaplan-Meier survival curves were used to explore 5-year survival and 12-year survival for BrCA-specific and all-cause survival at the state and regional levels. This was also stratified by race at the state and regional levels. Log rank test was used to assess the Kaplan-Meier plot with respect to the main exposure (race) within the four regions in SC.

Computing MIR

This study described BrCA disparities in SC among Blacks and Whites using MIRs by race for the four health regions and by 46 counties within SC. We proceeded to rank the four health regions by race from the worst to the best using MIRs. MIR were computed from Cancer incidence and mortality data which were obtained from the SC Community Access Network. In order to compare racial differences in BrCa MIRs in the four SC DHEC health regions, seven categories (for county maps) of BrCa MIRs were defined. First, the MIR were computed for Whites nationally (93) (i.e., for the US from the United States Cancer Statistics at the Centers for Disease Control and Prevention) as a

reference. The upper limit for Category 1 was the reference; the upper limit of Category 2 was 10% higher than the reference; the upper limit of Category 3 was 20% higher than the reference; the upper limit of category 4 was 30% higher than the reference; the upper limit of category 5 was 40% higher than the reference; the upper limit of category 6 was 50% higher than the reference and Category 7 consisted of MIRs >50% higher than the reference. This method of categorization and analysis was adapted from a previous study by Hebert et al. and Babatunde et al. (5, 38)

Computing MIR for four health regions:

BrCa MIRs by race (Black vs. White) were computed for years 2002-2010. Years 2002 to 2010 will be utilized to mirror the years of registry data that were obtained for the survival analyses. The age-adjusted incidence and mortality rates will first be calculated using incidence and mortality data from SCCCR. MIRs were stratified by race, specifically Blacks versus Whites.

Computing MIR for 46 counties:

BrCa MIRs by race (Black vs. White) were computed for years 1996-2016. Additional years were utilized to compute Black-White differences in MIR. This was not utilized for the MIR-Survival comparison because the years were outside the range for the survival data. This was utilized to visually inspect the extent of the Black-White disparities that exist when mapped in ArcGIS.

Interpreting the MIR

As a ratio with the mortality rate as the numerator and the incidence rate as the denominator, the MIR takes on numeric values ranging from 0 to 1. Values closer to 0

indicate more indolent cancers, whereas those closer to 1 indicate more aggressive cancers. The MIR, which has been shown to be highly insensitive to time-discordant incidence and mortality (152), does not take into account follow-up time and is not equivalent to Cox proportional hazards–type survival analysis, which is a truly multivariate technique that accounts for follow-up time. Similarly, the MIR cannot account for competing risk.

Mapping to visually compare MIR and Survival using ArcGIS 10.2

ArcGIS 10.2 was utilized to map BrCA MIRs by race (46 counties and 4 regions). MIR were categorized into seven levels (as described above) using the national MIR for BrCA as reference in county map. In order to map BrCA MIRs by race across the four health regions in SC, the categorizations were made based on the natural breaks created by ArcGIS. In ArcGIS, MIRs were mapped using choropleth maps that utilized graduated colors under quantities. The color ramp that were utilized for the maps was a color spectrum that consisted of green (the best/lower MIR) to red (the worst/higher MIR). Also, in ArcGIS, survival was symbolized using graduated symbols under quantities with a blue circle 22. The biggest circle size symbolized worse/lowest survival while the smallest circle size symbolized best/highest survival.

Correlation analyses to compare MIR and Survival using SAS 9.4

Survival-MIR correlation analyses were computed for all BrCA cases in each county/region utilizing SAS software. SAS® Version 9.4 (Cary, NC) was utilized to compute correlation analyses comparing MIR with 5- and 12-year survival. Correlation

analysis was also computed comparing hazard ratio with MIR. Pearson's correlation was utilized, and statistically significant correlation was determined using a p-value of 0.05.

Results

A total of 2155 breast cancer patients ($n_{\text{Whites}}=1557/72\%$; $n_{\text{Blacks}}= 598/28\%$) were reported in the study period. Table 1 shows the MIR by county by race. Graphically, in Figure 1, the map showed that Blacks were in the higher MIR categories in almost all counties while Whites were in the lower MIR categories in almost all the counties. Table 2 showed that the largest Black-White difference in all-cause 12-year and 5-year survival percentage was seen in Low Country region (15.5% and 8.0% respectively). The largest Black-White difference in BrCA specific 12-year and 5-year survival percentage was also seen in Low Country region (13.7% and 7.7% respectively). Although the lowest MIR overall was seen in the Low Country region when the entire population of Whites and Blacks were considered, the highest difference in Black-White MIR was also seen in the Low Country region.

The crude hazard ratio of mortality among Blacks compared with Whites was 1.42 (1.03, 1.95) for overall survival and 1.49 (1.04, 2.14) for BrCA specific survival (not presented in table). Multivariable cox proportional hazard that adjusted for cancer stage showed that the hazard ratio of mortality was 3.45 (1.64, 7.25) among Black women who lived in Low Country region of the state compared with White women who lived in Low Country region of the state when all-cause mortality was examined. A similar hazard ratio of mortality of 3.79 (1.68, 8.58) was seen among Black women who lived in Low Country region of the state compared with White who lived in same region when BrCA-specific mortality was examined. In the other three regions of the state (Midlands, Pee

Dee and Upstate); there were no statistically significant differences in hazard ratio that compared Blacks with Whites.

Table 3 presented the Pearson Correlation coefficients that compared MIR with 5-year survival, 12-year survival and adjusted hazard ratios for all-cause and BrCA-specific survival for all patients and stratified by race. When MIR for all cases were considered, there was statistically significant correlation between MIR for all cases and BrCA specific 12-year survival ($p: 0.01$; $r: -0.99$); between MIR for all cases and all-cause 12-year survival ($p: <0.01$; $r: -0.99$). The relationship showed that the higher the MIR, the lower the survival. Similar pattern was shown with MIR for Whites and survival but there was no statistically significant correlation between MIR for Blacks and their survival percentage. There was also significant correlation between the difference in White-Black BrCA specific 5-year survival and difference in Black-White MIR ($p: 0.03$; $r: 0.97$); between the Black versus White adjusted multivariable all-cause hazard ratio and difference in Black-White MIR ($P: 0.05$; $r: 0.95$).

Figure 2 graphically shows the relationship between survival and MIR for all cases while Figure 3 graphically shows same relationship among Whites. Both maps showed that there is a strong correlation between MIR and survival. The higher the survival percentage (positive and desired), the lower the MIR (positive and desired). Since this relationship was not seen among Blacks, this was not mapped. Figure 4 graphically shows the relationship between the Black-White difference in MIR and White-Black difference in BrCA specific 5-year survival ($p: 0.03$; $r: 0.97$). This showed that survival was highest where the MIR difference was lowest (Midlands region). Also,

in Figure 4, all-cause hazard ratio for Blacks versus Whites was highest in the Low Country region where the Black-White difference was highest.

The map showed that Blacks were in the higher MIR and lower survival categories while Whites were in the lower MIR and higher survival categories. There were multiple statistically significant correlations between MIR and survival overall; MIR and survival among Whites; and Black-White difference in MIR versus Black-White difference in survival (all p-values were <0.05). Low Country region was identified as the region with worse Black-White MIR and survival disparity.

Discussion

This study found that Blacks were in the higher/worse MIR categories in most of the counties while Whites were in the lower/better MIR categories in most of the counties. The largest Black-White difference was seen in Low Country region. While the lowest/better MIR overall was seen in the Low Country region when the entire population of Whites and Blacks were considered, the highest difference in Black-White MIR was also seen in the Low Country region. When MIR for the entire population were considered, there was statistically significant correlation between MIR and survival (p: 0.01; r: -0.99); between MIR for all cases and all-cause 12-year survival (p: <0.01 ; r: -0.99). The relationship showed that the higher the MIR, the lower the survival. Similar pattern was shown with MIR for Whites and survival but there was no statistically significant correlation between MIR for Blacks and their survival percentage. Additionally, we found that there was also significant correlation between the difference in White-Black BrCA specific 5-year survival and difference in Black-White MIR (p:

0.03; r : 0.97); between the Black versus White adjusted multivariable all-cause hazard ratio and difference in Black-White MIR (P : 0.05; r : 0.95).

Recommendations have been made for cancer surveillance programs to use MIRs to monitor disparities across racial/ethnic groups and geographic regions (5, 10-14, 38) as a proxy for survival and our study helped to assess the effectiveness of MIR as a proxy for survival using cancer-specific survival among BrCA patients, especially in South Carolina where there is marked Black-White disparity. (38) Our finding showed that MIR mirrors BrCA survival across the health regions. Asadzadeh et al computed the validity of the MIR as a proxy for site-specific cancer survival in 2010 in which relative survival data was utilized. (162)

We have shown that despite the known drawbacks of MIR such as not accounting for censoring and loss to follow up, counting the mortality from previous years while using incidence from the current year, inability to account for covariates and competing risks; the MIR is still a fair reflection of survival and racial disparities. The MIR may therefore be utilized as a proxy for survival studies which are a more complex, time-consuming and expensive analyses that require more skills to carry out. Using MIR is less time-consuming, less expensive and requires fewer skills to carry out. (5) Therefore, the potential utility of the MIR in cancer surveillance programs for monitoring disparities across racial/ethnic groups and geographic regions is substantial, as shown by previous studies. (5, 10, 12, 14, 38) and our current study.

Our study also found that the Black-White MIR difference is highest in the Low Country region which is directly correlated with White-Black 5-year survival difference.

This also agrees with the use of the MIR as a surveillance tool in past studies which underscores the point that SC exhibits more extreme racial differences in cancer incidence, mortality and MIR than other states or the nation. (30-37) Specifically, in a previous study in SC, the MIR helped highlight regions where this disparity is highest (38). For example, in this past study, the Pee Dee region in SC have the highest MIR disparity, where the MIRs of Blacks are 3.1 and 3.0 times higher, respectively, than those of Whites. Also, in our current study, the MIR for Blacks was highest in the Pee Dee region (0.217) although the Black-White disparity was highest in the Low Country region.

The Pee Dee region is known for its lower socioeconomic status, rurality and being medically underserved (5). Additionally, in four of the 12 counties in the Pee Dee regions (Dillon, Lee, Marlboro and Williamsburg), over 40% of adults report a BMI of 30 or more (153). Similarly, the percentage of adults aged 20 and over reporting no leisure-time physical activity was greater than 30% in seven counties (Chesterfield, Darlington, Dillon, Lee, Marion, Marlboro and Sumter) out the 12 counties in the Pee Dee region (153). The usefulness of the MIR in racial disparity was also buttressed by the study by Wagner et al. that described racial cancer disparities and their potential geographical determinants by calculating, comparing and mapping MIRs throughout the state of Georgia (GA, United States). This study found that Blacks in GA had more fatal cancers than Whites for all cancer sites evaluated (10). Additionally, examining the MIR helped to highlight health regions where this disparity is highest. (38)

Our study also showed the importance of the assessment of racial disparity in MIR and survival at the regional level, a step beyond the state level. We found that the

disparity is highest in the Low Country region. This finding that highlighted the region with the highest disparity in SC may be useful to help inform policy direction in the SC's state BCN program which is an early detection program for breast and cervical cancer (41, 141).

Obesity rate may be one of the factors affecting the racial disparities in the Low Country region of SC. In SC, it has been hypothesized that comorbid illnesses and obesity could be the driver of cancer racial disparity. (157) Obesity and comorbid illnesses affect Blacks in SC at a rate that is above the national average. (157, 158) In 2018 report, SC has the 10th highest adult obesity rate in the US, this is up from being the 13th highest in 2016. Comparing these figures to that of 2000 and 1999 (21.1% and 12% respectively), the weight gain problem appears to be persistently on the rise in SC. (157, 158) The regional sub-population of the Gullahs may also be one of the factors affecting the racial disparities in the Low Country region of SC. The Gullahs are a unique Black sub-population known as the that live and reside in the farming and the fishing communities along SC's coastal areas. (157)

The Gullah community are geographically isolated and previous studies has shown that they experienced limited access to health care and that they are at a higher risk of cardiometabolic risk factors for diabetes mellitus. (160, 161) Socioeconomic status (SES) has been identified as one of the main drivers of racial disparities in BrCA mortality, as women in low socioeconomic levels tend to present with more advanced-stage BrCA, which usually has poorer prognosis (71, 80). Specifically, in Charleston, the median income in 2015 for a white family in Charleston–North Charleston was more than double for black families, \$64,553 compared to \$29,799.

A previous report shows that predictors that are environmental in nature affect health and disparity, (59) but the influence of geographical factors has not been well explored among younger women. This is particularly important because young Black women (less than 65 years old) present with relatively more fatal BrCA, leading to higher mortality among this group. (30, 40) Most studies on the MIR have been on international comparisons of the MIR based on cancer management outcomes, health care systems ranking, national healthcare disparities, across several countries. (162-169) We have added to the literature that MIR can also be applied locally for the purpose of surveillance and assessment of racial disparities.

To our knowledge, this is the first study that seeks to directly compute MIR by health regions and compare this ranking with a ranking produced by five-year and 12-year survival time to further substantiate the usefulness of the MIR in resource-poor settings and in quick decision making to identify areas that need urgent interventions. This is also the first time that the MIR will be utilized to assess BrCa disparities in addition to the direct sensitivity analyses comparing MIR with survival analyses both on the state and regional level. Identifying predictors of racial differences in survival by regions is also unique as findings has the potential to help guide more result-oriented navigation efforts. Overall, the study population (SC) in this study is unique because of the high proportion of SC residents that live in rural areas and the high racial disparity found in SC in other studies. (38, 170) One weakness however, of this study is that we did not assess the Hispanic population because the BrCA patients had very low representation in SC. Another weakness is that the data that we utilized for survival analyses was limited to BrCA patients below the age of 65 years while the data that we utilized for the MIR

contained all BrCA patients (this was necessary to get an age-adjusted mortality and incidence). Because we got the incidence and mortality data from the South Carolina Community Assessment Network/Department of Health and Environmental Control website, there was no way to remove the 65+ from the data and still get an age-adjusted rate.

This study finds that the health region ranking utilizing the MIR was highly correlated with survival time in the overall population and among White population. It may therefore be preferable to use the cheaper, faster and less time-consuming MIR, which also requires fewer skills, to identify geographic disparities and rank health regions to identify areas that require urgent attention/interventions. Additionally, the MIR is cheap and easy to compute from existing relatively complete data. The MIR can be used as a surrogate measure for a more expensive and time-consuming survival studies (38). Additional studies with larger sample size may help to understand the relationship between MIR and survival among Black population. Cancer surveillance programs may use the MIR to monitor disparities across racial/ethnic groups and geographic regions going forward. MIRs have the potential to serve as an indicator of the long-term success of cancer surveillance programs.

Table 6.1: MIR by race by county in SC (1996-2016)

County	MIR Blacks	MIR Whites	County	MIR Blacks	MIR Whites
Abbeville	0.19	0.12	Greenwood	0.20	0.16
Aiken	0.23	0.16	Hampton	0.25	0.17
Allendale	0.29	0.19	Horry	0.26	0.15
Anderson	0.17	0.14	Jasper	0.28	0.16
Bamberg	0.24	0.16	Kershaw	0.19	0.15
Barnwell	0.26	0.14	Lancaster	0.24	0.13
Beaufort	0.20	0.12	Laurens	0.21	0.15
Berkeley	0.15	0.13	Lee	0.30	0.16
Calhoun	0.18	0.19	Lexington	0.19	0.14
Charleston	0.20	0.11	McCormick		0.12
Cherokee	0.26	0.18	Marion	0.24	0.23
Chester	0.27	0.18	Marlboro	0.24	0.15
Chesterfield	0.19	0.18	Newberry	0.21	0.14
Clarendon	0.19	0.18	Oconee	0.26	0.15
Colleton	0.18	0.15	Orangeburg	0.24	0.14
Darlington	0.26	0.17	Pickens	0.22	0.12
Dillon	0.24	0.19	Richland	0.20	0.13
Dorchester	0.20	0.12	Saluda	0.29	0.19
Edgefield	0.26	0.16	Spartanburg	0.23	0.15
Fairfield	0.20	0.15	Sumter	0.19	0.16
Florence	0.26	0.15	Union	0.23	0.18
Georgetown	0.20	0.14	Williamsburg	0.27	0.18
Greenville	0.20	0.13	York	0.21	0.15

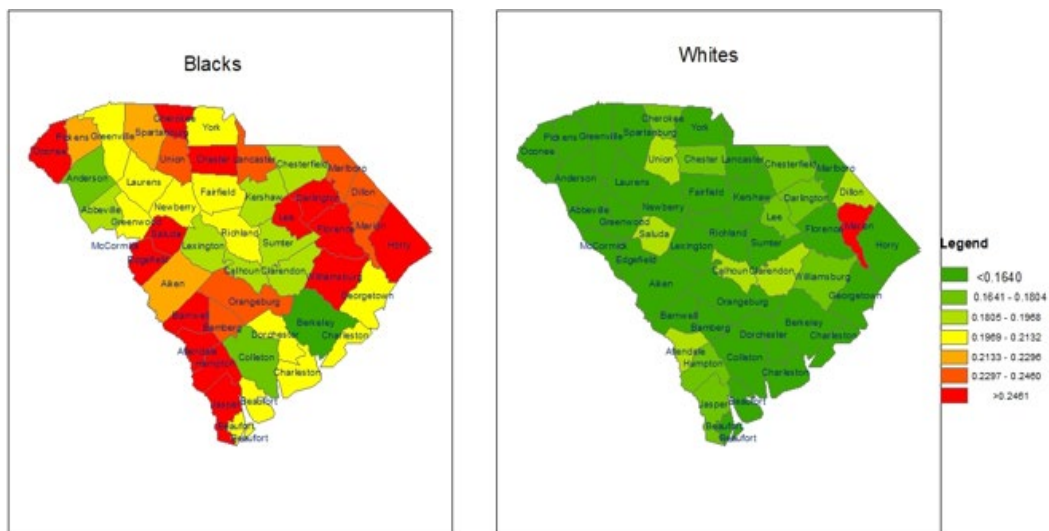


Figure 6.1: Racial disparities in mortality-to-incidence ratio of Breast Cancer for Blacks and Whites in South Carolina

Table 6.2 Breast Cancer: ^aSurvival Proportion and Mortality to Incidence Ratio (MIR) (2002-2010) in South Carolina by Race and Health Region

	All	White	Blacks	White-Black	All	White	Black	White-Black
^b Health Region	All Cause 12YS (%)	All Cause 12YS (%)	All Cause 12YS (%)	All Cause 12YS (%)	All Cause 5YS (%)	All Cause 5YS (%)	All Cause 5YS (%)	All Cause 5YS (%)
^c LC	89.3	94.3	78.8	15.5	95.0	97.7	89.7	8.0
MD	85.3	84.9	90.0	-5.1	94.8	94.9	94.3	0.6
PD	78.5	82.7	75.7	7.0	93.7	93.4	95.0	-1.6
UP	87.5	88.1	84.1	4.0	95.8	96.1	92.1	4.0
	All	White	Blacks	White-Black	All	White	Black	White-Black
^b Health Region	BrCA Sp 12YS (%)	BrCA Sp 12YS (%)	BrCA Sp 12YS (%)	BrCA Sp 12YS (%)	BrCA Sp 5YS (%)	BrCA Sp 5YS (%)	BrCA Sp 5YS (%)	BrCA Sp 5YS (%)
LC	91.3	95.6	81.9	13.7	95.5	98.0	90.3	7.7
MD	89.3	89.0	90.0	-1.0	95.6	95.8	95	0.8
PD	82.9	87.4	80.1	7.3	95.2	95.5	94.7	0.8
UP	90.7	90.7	92.1	-1.4	96.1	96.1	92.1	4
	All	White	Blacks	White-Black	HR AC		HR BrCA	
^b Health Region	MIR	MIR	MIR	MIR	Black	White	Black	White
LC	0.155	0.133	0.207	0.074	^c 3.45	1.00	^g 3.79	1.00
MD	0.163	0.145	0.208	0.063	^d 0.68	1.00	^a 0.72	1.00
PD	0.177	0.151	0.217	0.066	^e 0.99	1.00	^f 0.94	1.00
UP	0.159	0.145	0.214	0.069	^c 1.43	1.00	^g 1.32	1.00

^a5YS: 5-year survival; 12YS: 12-year survival; BrCA: Breast Cancer.

^bLC: LowCountry region; MD: Midland region; PD: PeeDee region; UP: Upstate region.

^cAdjusted for stage

^dAdjusted for stage and grade.

^eAdjusted for stage, grade and age

^fAdjusted for age and grade

^gCrude HR reported because no additional variable met entry into the model for adjustment

Table 6.3: Correlation between ^aSurvival Proportion and Mortality to Incidence Ratio (MIR) (2002-2010) in South Carolina among Breast Cancer Patients by race and region.

Survival Variable	MIR Variable	p-value	Pearson Correlation Coefficient
Survival by MIR for all patients			
^b BrCA Specific 12 YS (All patients)	MIR (All patients)	0.01	-0.99
All Cause 12 YS (All patients)	MIR (All patients)	<0.01	-0.99
BrCA Specific 5YS (All patients)	MIR (All patients)	0.37	-0.63
All Cause 5YS (All patients)	MIR (All patients)	0.15	-0.85
Black survival by Black MIR			
Black BrCA Specific 12 YS	Black MIR	0.85	0.15
Black All Cause 12 YS	Black MIR	0.52	-0.48
Black BrCA Specific 5 YS	Black MIR	0.62	0.38
Black All Cause 5 YS	Black MIR	0.45	0.55
White survival by White MIR			
White BrCA Specific 12 YS	White MIR	0.02	-0.976
White All Cause 12 YS	White MIR	0.03	-0.97
White BrCA Specific 5 YS	White MIR	0.02	-0.97
White All Cause 5 YS	White MIR	0.06	-0.94
Survival disparity by MIR disparity			
White-Black BrCA Specific 12 YS	Black-White MIR	0.30	0.70
White-Black All Cause 12 YS	Black-White MIR	0.09	0.91
White-Black BrCA Specific 5YS	Black-White MIR	0.03	0.97
White-Black All Cause 5 YS	Black-White MIR	0.11	0.88
Hazard Ratio by MIR disparity			
All Cause Hazard Ratio Black versus White	Black-White MIR	0.05	0.95
BrCA Specific Hazard Ratio Black versus White	Black-White MIR	0.07	0.93

^a5YS: 5-year survival; 12YS: 12-year survival;

^bBrCA: Breast Cancer

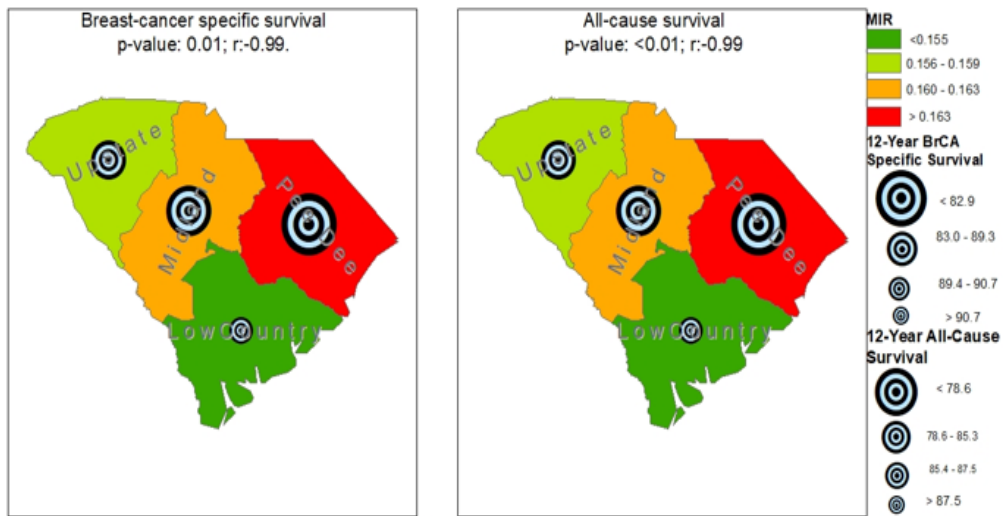


Figure 6.2: Mortality-to-incidence ration of Breast Cancer for South Carolina compared with 12-year survival

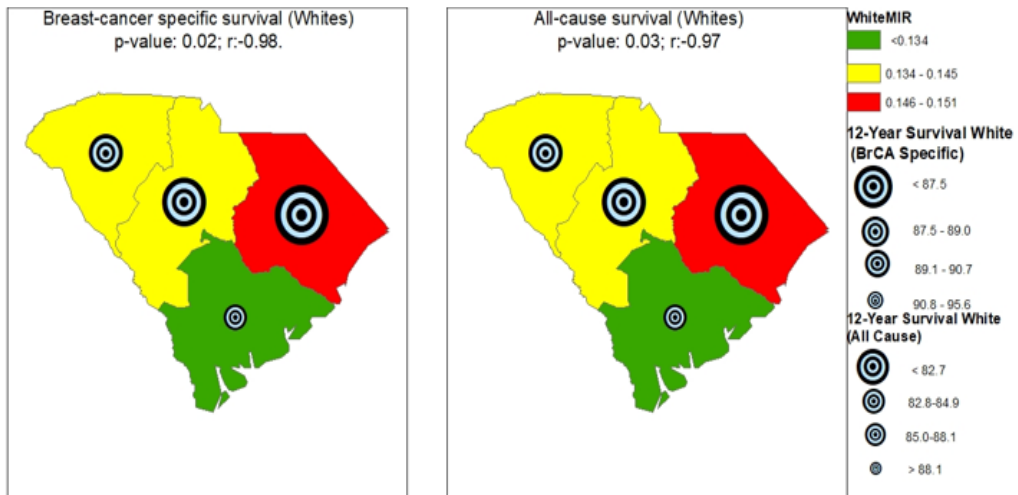


Figure 6.3: Mortality-to-incidence ratio of White Breast Cancer patients in South Carolina compared with White 12-year survival

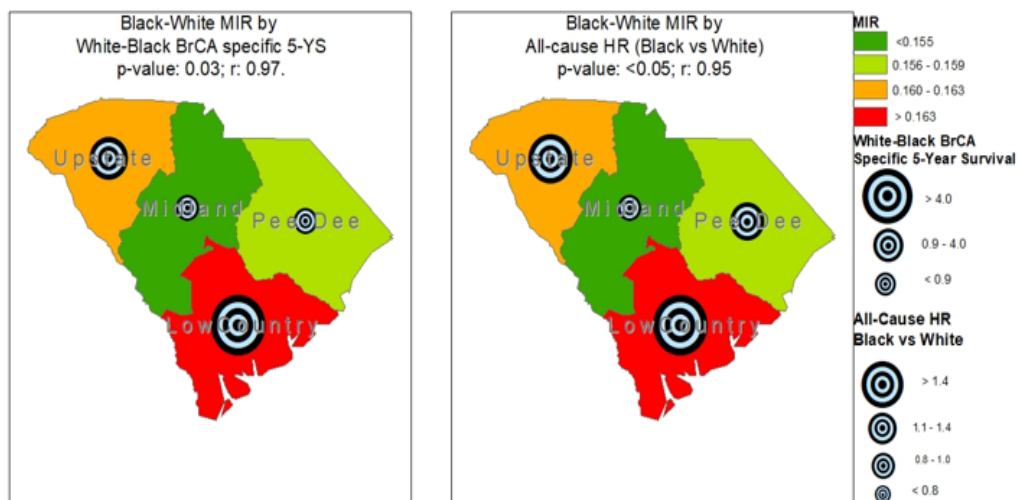


Figure 6.4: Racial disparity in Mortality-to-incidence of Breast Cancer in South Carolina compared with 5-year survival and all-cause Hazard Ratio

CHAPTER 7

OVERALL SUMMARY

Objectives

The aims of this study were:

1. To assess racial disparities in BrCA treatment time in South Carolina (SC) by comparing diagnosis-to-treatment times for the various forms of treatment in Blacks and Whites with BrCA and to assess related effect modifiers. We hypothesize that the diagnosis-to-treatment wait time is higher among Blacks compared to Whites for all BrCA treatment types in SC.
2. To analyze the breast cancer-specific and overall survival in SC, as well as by four health regions and to assess the factors (confounders and effect modifiers) affecting survival among Black and Whites in SC overall. We hypothesize that treatment and mortality outcomes will be worse for Blacks who live in Pee Dee, which are characterized by lower socioeconomic status, and will be better in Midlands and Low Country because of the major hospital systems available in these regions.
3. To assess the effectiveness of MIR as a proxy for survival and geospatially investigate racial disparity among BrCA patients. This was achieved by comparing the MIR methodology with survival methodology in assessing racial

4. BrCA disparities across the four health regions in SC. We hypothesize that the findings from MIR by regions will be similar to the survival analyses by regions.

Main Findings

This study demonstrated that there was a longer diagnosis-to-treatment time for all treatment modalities for Blacks when compared with Whites. Late receipt of AHT was higher among blacks that were unmarried, received late surgery, and not a participant of the BCN. We also found that late receipt of surgery was higher among blacks that were unmarried, lived in urban areas and those who lived less than 10 miles to their health care provider. The only sub-group where whites had a later receipt of treatment was for post-surgery radiation among hormone receptor negative BrCA patients.

In addition to showing that there were longer diagnosis-to-treatment time in which has been demonstrated from previous studies, (18, 22, 26, 74, 128) we were able to add the following to the racial disparity discussion: the impact of being unmarried, living in urban areas, enrolment in BCN, and distance on late receipt of treatment. This study also showed the positive relationship between late receipt of surgery and time to AHT demonstrating that those who are late to receive one form of treatment are likely to be late at the receipt at other forms of treatment. The use of the findings in this paper has the potential to further enhance the understanding of navigation of health care process and strengthen navigation efforts aimed at linking women with BrCA to care especially among blacks thereby reducing racial disparities.

The Kaplan Meier model found that there was a statistically significant difference between Blacks and Whites in the state of SC overall, however, among the 4 health regions, only the Low Country region had statistically significant difference with

mortality higher among Blacks. This difference is seen as early as 3 years and it continues to widen till 12 years. Also, in the Kaplan Meier model, the Low Country region had higher BrCA survival than the other three regions, but it also demonstrated the widest racial disparity. In Cox Proportional multivariable model, we also showed that hazard ratio of mortality was 3.45(1.64,7.25) among Black women who lived in Low Country region of the state compared with White women who lived in Low Country region of the state when all-cause mortality was examined; and 3.79 (1.68, 8.58) was seen among Black women who lived in Low Country region of the state compared with White who lived in same region when BrCA-specific mortality was examined. Multivariable Cox proportional hazard that adjusted for cancer stage and grade showed that the hazard ratio of mortality was 1.53(1.04,2.26) among Black women who lived in urban areas compared with White women who lived in urban areas for all-cause mortality.

We also found that Blacks were in the higher/worse MIR categories in most of the counties while Whites were in the lower/better MIR categories in most of the counties. The largest Black-White difference was seen in Low Country region. While the lowest/better MIR overall was seen in the Low Country region when the entire population of Whites and Blacks were considered, the highest difference in Black-White MIR was also seen in the Low Country region. When MIR for the entire population were considered, there was statistically significant correlation between MIR and survival ($p: 0.01$; $r: -0.99$); between MIR for all cases and all-cause 12-year survival ($p: <0.01$; $r: -0.99$). The relationship showed that the higher the MIR, the lower the survival. Similar pattern was shown with MIR for Whites and survival but there was no statistically significant correlation between MIR for Blacks and their survival percentage.

Additionally, we found that there was also significant correlation between the difference in White-Black BrCA specific 5-year survival and difference in Black-White MIR (p: 0.03; r: 0.97); between the Black versus White adjusted multivariable all-cause hazard ratio and difference in Black-White MIR (P: 0.05; r: 0.95).

Conclusions

In conclusion, late receipt of AHT was higher among blacks that were unmarried, received late surgery, and not a participant in BCN. We also found that late receipt of surgery was higher among blacks that were unmarried, lived in urban areas and those who lived less than 10 miles to their health care provider. There is a longer diagnosis-to-treatment time in receipt of AHT between blacks and white that are not on BCN but no difference between blacks and white on BCN, it therefore suggests that, perhaps the BCN is helping to close the racial disparity gap between whites and blacks or those who are on BCN have other factors that is driving the racial disparities.

We also noted found that mortality was higher among Blacks who lived in the Low Country region of the state and among Blacks who lived in urban areas. Although the Low Country region had the highest 12-year survival among a combination of Whites and Black population, relative to other three health regions, it demonstrated the highest Black-White racial disparity relative to the other three regions. Despite the awareness and funding dedicated to closing the racial gap in cancer therapy, it is discouraging to note that racial disparities persist in BrCA mortality (60, 61). Navigation programs and other available programs aimed at reducing racial disparities may benefit from these finding by committing more resources that are culturally acceptable to the Low Country region of

SC. Considering that Low Country seemed to have the best mortality outcome (when combined data is used) but the worse Black-White disparity, the Low Country region may benefit from specific community-oriented interventions similar to the community COMPASS project (157) that has the potential to close this gap.

Our study also showed that the health region ranking utilizing the MIR was highly correlated with survival time in the overall population and among White population. It may therefore be preferable to use the cheaper, faster and less time-consuming MIR, which also requires fewer skills, to identify racial disparities and rank health regions to identify areas that require urgent attention/interventions. Additionally, the MIR is cheap and easy to compute from existing relatively complete data. The MIR can be used as a surrogate measure for a more expensive and time-consuming survival studies (38).

Recommendations

The relationship between being on BCN and diagnosis-to-treatment time in receipt on AHT will benefit from future studies as it will be important to understand the reason for the longer time among those not on BCN. To improve overall timely receipt of AHT, efforts need to be directed at Black BrCA patients that are not married, not on BCN and received late surgery. To improve overall timely receipt of surgery, efforts need to be directed at Black BrCA patients that are not married, lived in urban areas and lived ≤ 10 miles from health providers.

To reduce racial disparity gap in survival in SC, Black breast cancer patients that live in Low Country region and those that live in urban areas may benefit from more intense navigation efforts directed at early detection and linkage to receipt of breast

cancer treatments. Future studies are also required to identify the potential, biological, patient-, physician-, and healthcare-system-related factors underlying our observations and optimize cancer care among Blacks in SC particularly in the Low Country region. Additionally, the state of SC will benefit from future studies to assess the regional disparities in other common cancers to identify if this trend seen in the Low Country specific to BrCA or other cancers in order to inform future implementation regional appropriate policies that may help to close this gap.

Additional studies with larger sample size may help to understand the relationship between MIR and survival among Black population. Cancer surveillance programs may use the MIR to monitor disparities across racial/ethnic groups and geographic regions going forward. MIRs have the potential to serve as an indicator of the long-term success of cancer surveillance programs.

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